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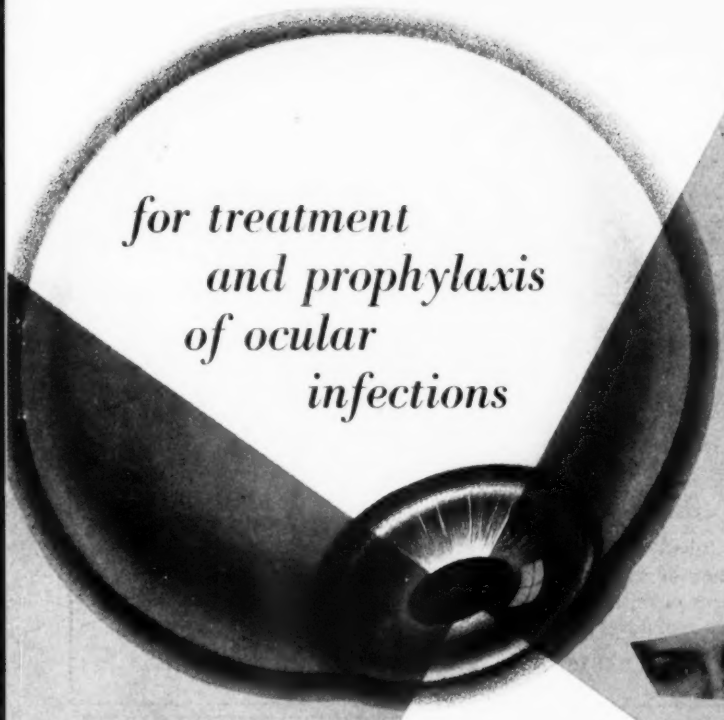

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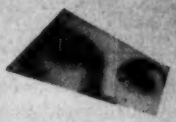

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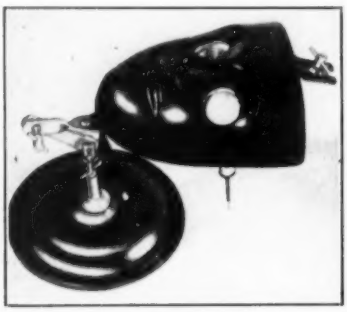

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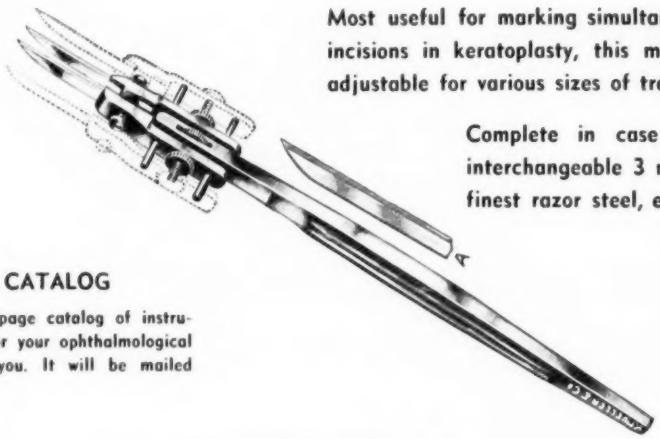

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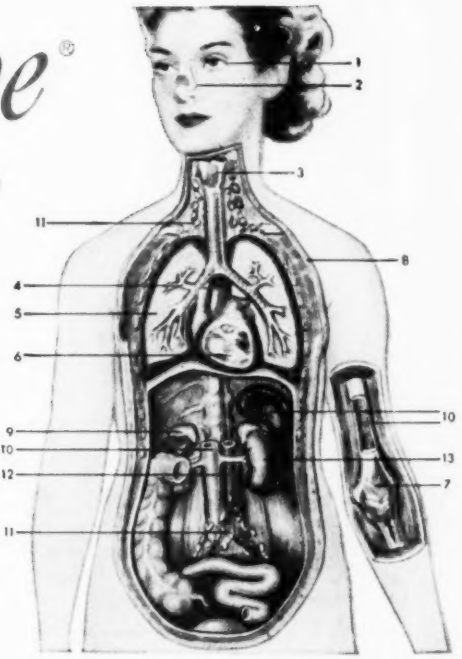

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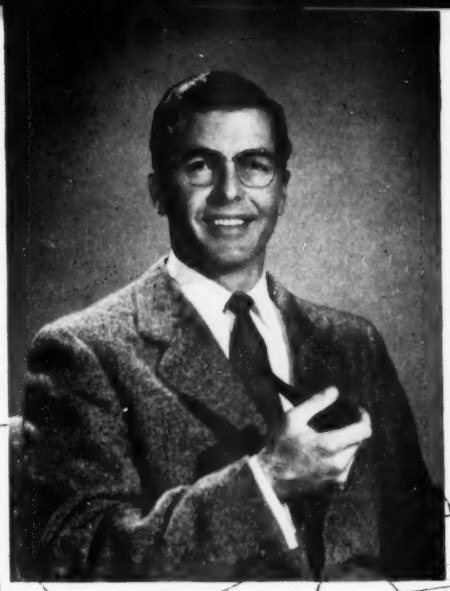

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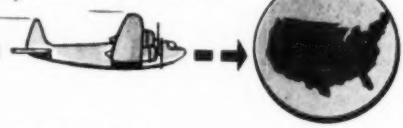

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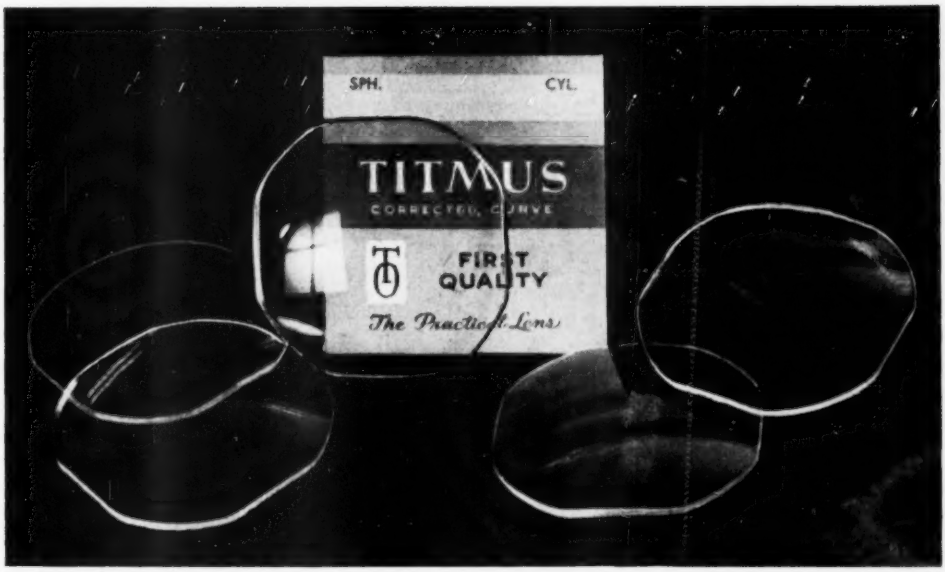

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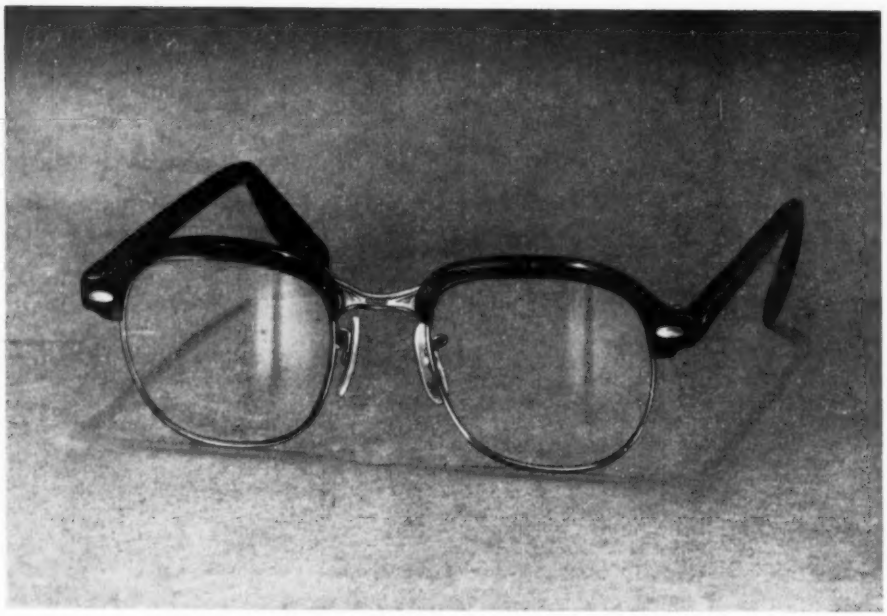

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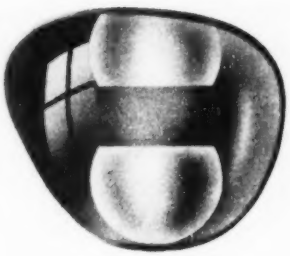

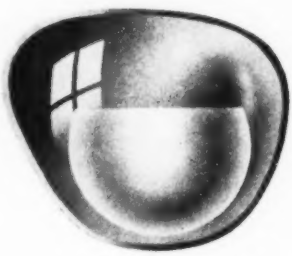

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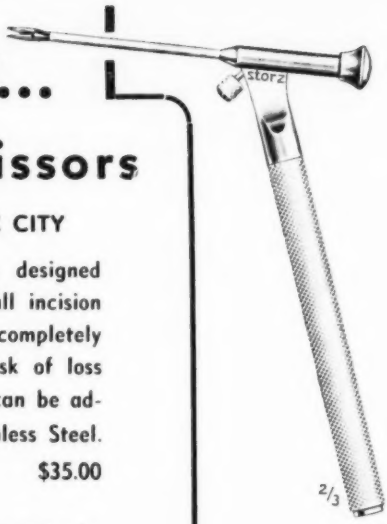

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EVALUATION OF OPHTHALMOSCOPIC CHANGES OF HYPERTENSION AND ARTERIOLAR SCLEROSIS

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PHILADELPHIA

FOR THE subject of this lecture, I have selected the ophthalmoscopic changes associated with hypertension and arteriolar sclerosis. I shall emphasize certain concepts which are of value in interpreting the ophthalmoscopic signs of these diseases and describe a system of grading these changes which has proved useful to me.[1] Although exhaustive descriptions of these changes are available, the literature on their significance is at times confusing and in many instances contradictory.

The three most important reasons for this state of our knowledge are the following: (1) failure to realize that most of the retinal arterial tree is arteriolar in nature, a point emphasized repeatedly by Wagener and associates[2] and Friedenwald[3]; (2) failure to utilize knowledge made available by the pathologist and the physiologist of the changes occurring in vessels of similar size elsewhere in the body; (3) inaccurate use of the term "arteriosclerosis." Arteriosclerosis is a general term which includes several types of degenerative arterial disease; yet throughout the ophthalmologic literature little attempt has been made to be specific when changes observed in the retinal vessels were described or interpreted. As a result, the terms "arteriosclerosis," "arteriolar sclerosis," " arteriolosclerosis," "atherosclerosis," and even "sclerosis" have often been used interchangeably.

The anatomical characteristics of the retinal arteries have not been sufficiently emphasized in most papers and textbooks dealing with the retinal changes in vascular disease. The retinal arterial tree is arteriolar in nature except for the central

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From the Department of Ophthalmology, Hospital of the University of Pennsylvania, University of Pennsylvania School of Medicine, the Graduate School of the University of Pennsylvania, and the Children's Hospital of Philadelphia.

1. Scheie, H. G.: Retinal Changes Associated with Hypertension and Arteriosclerosis, Ill. M. J. **101**:126, 1952.

2. Wagener, H. P.: Retinitis of Malignant Hypertension, Tr. Am. Ophth. Soc. **25**:349, 1927. Wagener, H. P.; Keith, N. M., and Kernohan, J. W.: Syndrome of Malignant Hypertension, Arch. Int. Med. **41**:141, 1928. Wagener, H. P.: Clinical Interpretation of Retinal Vascular Lesions in Hypertension and Nephritis, Pennsylvania M. J. **40**:705, 1937. Keith, N. M.; Wagener, H. P., and Barker, N. W.: Some Different Types of Essential Hypertension: Their Course and Prognosis, Am. J. M. Sc. **197**:332, 1939. Wagener, H. P.: Retinopathy in Glomerulonephritis, ibid. **209**:257, 1945.

3. Friedenwald, J. S.: Retinal and Choroidal Arteriosclerosis, in Ridley, F., and Sorsby, A.: Modern Trends in Ophthalmology, New York, Paul B. Hoeber, Inc., 1940, p. 77; 82.

artery and possibly some of its large branches near the disk. A true artery possesses an internal elastic lamina and a well-developed muscular coat, while an arteriole has no elastic lamina and the muscle layer is not continuous. The central artery, according to Friedenwald,[3] begins to show marked alteration in its structure after passing through the lamina cribrosa of the sclera, where it first loses the characteristics of a true artery. The internal elastic lamina becomes rapidly reduced in thickness and disappears entirely at the first or second bifurcation. The muscular coat becomes thin and the muscle fibers lose continuity, to become separated from one another by small gaps. By the time the first or second bifurcation is reached, the retinal arterial tree has become arteriolar in nature.

The fact that arteriosclerosis is a general term which includes several entities, not all of which affect arterioles, should be kept in mind when one is evaluating the fundus of a patient for evidence of arterial disease. Some types of arteriosclerosis occur only in large arteries; some, only in arterioles, and some, throughout the

*Classification of Arteriolar Sclerosis**

Type	Etiology	Size of Vessel Involved	Ocular Involvement
1. Regenerative intimal thickening	Involution	Any size	Retinal atrophy; optic atrophy
2. Elastic intimal thickening	Age change; hypertension	Medium-sized and small arteries	Central artery, not seen ophthalmoscopically
3. Ectasia	Senility	Large arteries only	None
4. Medial calcification (Mönckeberg's sclerosis)	Age change	Large arteries of extremities	None
5. Intimal atherosclerosis	Age; heredity	True arteries of any size	Central artery and branches near disk
6. Arteriolar sclerosis	Hypertension	Arterioles	Entire retinal arterial tree

* After Bell.[4]

arterial system. Obviously, only those types producing changes in arterioles or very small arteries could produce alterations in the arterial system of the retina which might be visible ophthalmoscopically. Bell [4] recognized six different types of arteriosclerosis, each having its own significance (Table).

1. Regenerative intimal thickening. Regenerative thickening of the intima occurs in atrophic organs, where, owing to atrophy or disuse, there is diminished demand for blood flow. The intima of the artery therefore thickens to narrow the lumen, and occasionally to obliterate it (Fig. 1*A*). The newly formed intimal tissue is loose and fibrillar in structure. The process can occur in arteries of any size.

2. Elastic intimal thickening. Elastic thickening of the intima occurs normally throughout life. The internal elastic lamina of medium and small-sized arteries reduplicates until in advanced life it usually consists of two or three layers (Fig. 1*B*). This process is accentuated in prolonged, severe hypertension, in which the internal elastic lamina may be 10 or 12 layers in thickness. This probably represents a compensatory response to the increased intra-arterial pressure. The intima is then composed mainly of elastic tissue.

4. Bell, E. T.: A Text-Book of Pathology, Ed. 5, Philadelphia, Lea & Febiger, 1944, pp. 594-600.

3. Senile ectasia. Ectasia is a type of arteriosclerosis that is a disease of senility. It is limited to the aorta and some of the larger arteries. The vessels become dilated, and their walls are thinned, owing to multiple ruptures of the elastic layers.

4. Medial calcification (Mönckeberg's sclerosis). Medial calcification, which first involves the arteries of the lower extremities, is usually found in adult life (Fig. 2). It occurs later in the upper extremities. It can be associated with intimal atherosclerosis but is apparently a distinct disease process.

5. Intimal atherosclerosis. Intimal atherosclerosis is a plaque-like disease of the intima which affects true arteries of any size. The cause is unknown.

6. Arteriolar sclerosis. Arteriolar sclerosis, as the term implies, is a disease affecting arterioles. It is associated with hypertension and is believed to occur as a result of it.

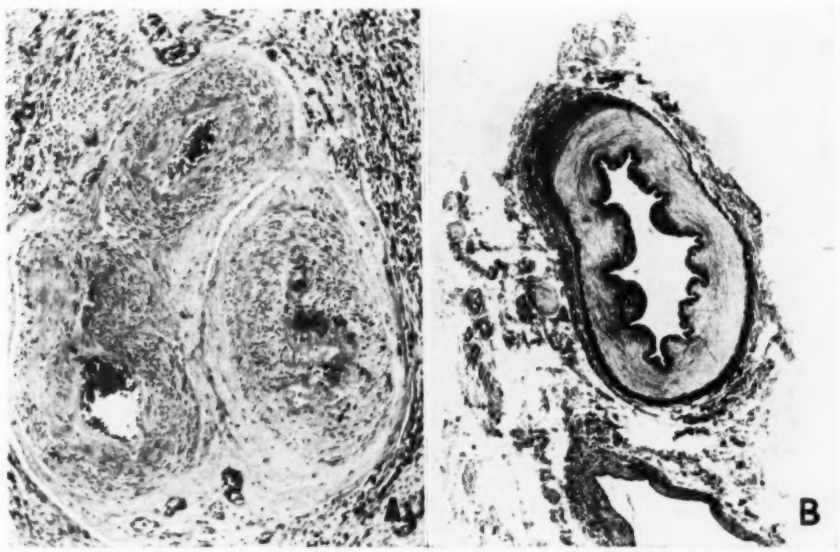

Fig. 1.—*A*, cross section of uterine arteries showing regenerative thickening of the intima. *B*, cross section of artery showing reduplication of elastic lamina.

Of the six entities in Bell's [4] classification, senile ectasia and medial calcification do not involve the retinal arterial tree, since they involve only large arteries. The remaining four types affect small arteries or arterioles and theoretically might occur in the retinal vessels. One, elastic intimal thickening, while it may involve these vessels, produces no characteristic ophthalmoscopic signs. The other three are accompanied by characteristic regenerative thickening of the intima, or "obliterative endarteritis," which occurs in vessels or organs undergoing atrophy or involution, where there is diminished need for blood flow. Friedenwald [3] suggested that this might explain the attenuated retinal arterial tree found with retinitis pigmentosa and certain types of optic nerve atrophy. Intimal atherosclerosis and arteriolar

sclerosis are the two commonest types of arterial disease which occur in the retinal vessels. Although each is a distinct disease entity and each causes a characteristic ophthalmoscopic picture, they are frequently confused in the ophthalmologic literature, the two terms often being used interchangeably. They should be carefully differentiated, however, because of their different nature and significance.

Fig. 2.—Cross section of artery of lower extremity showing calcification of media.

INTIMAL ATHEROSCLEROSIS

General and Ophthalmoscopic Manifestations.—Intimal atherosclerosis is a disease of the intima, which usually appears first in the aorta, often as early as the second or third decade of life, and is nearly always present in persons 40 to 50 years of age; but the severity will vary. The lower part of the abdominal aorta or

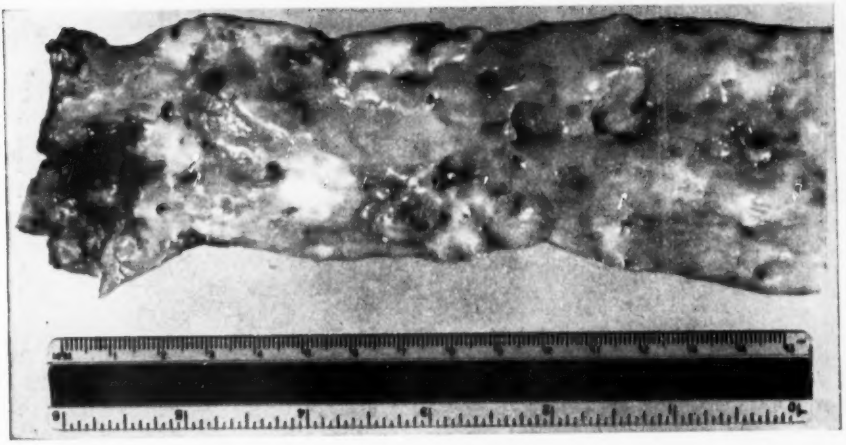

Fig. 3.—Photograph of aorta showing extensive lesions of intimal atherosclerosis.

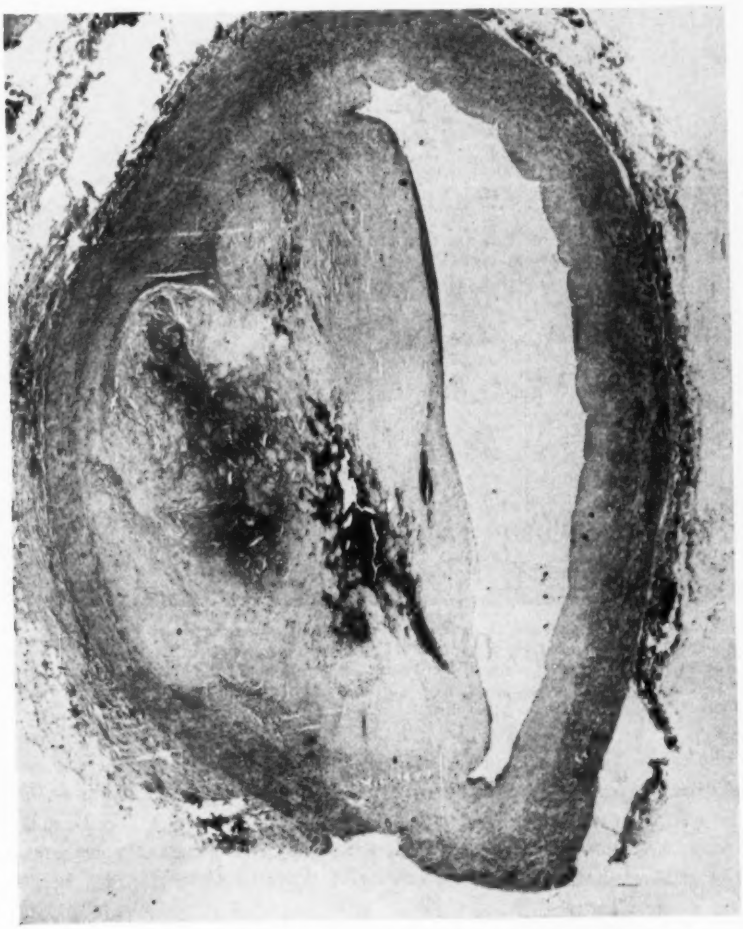

Fig. 4.—Cross section of aorta showing large atheroma.

the site of the ductus arteriosus is characteristically first involved. With increasing age, the intimal lesions become more widely distributed throughout the arteries of the body (Fig. 3). It is by far the most frequent type of arterial disease seen in man.

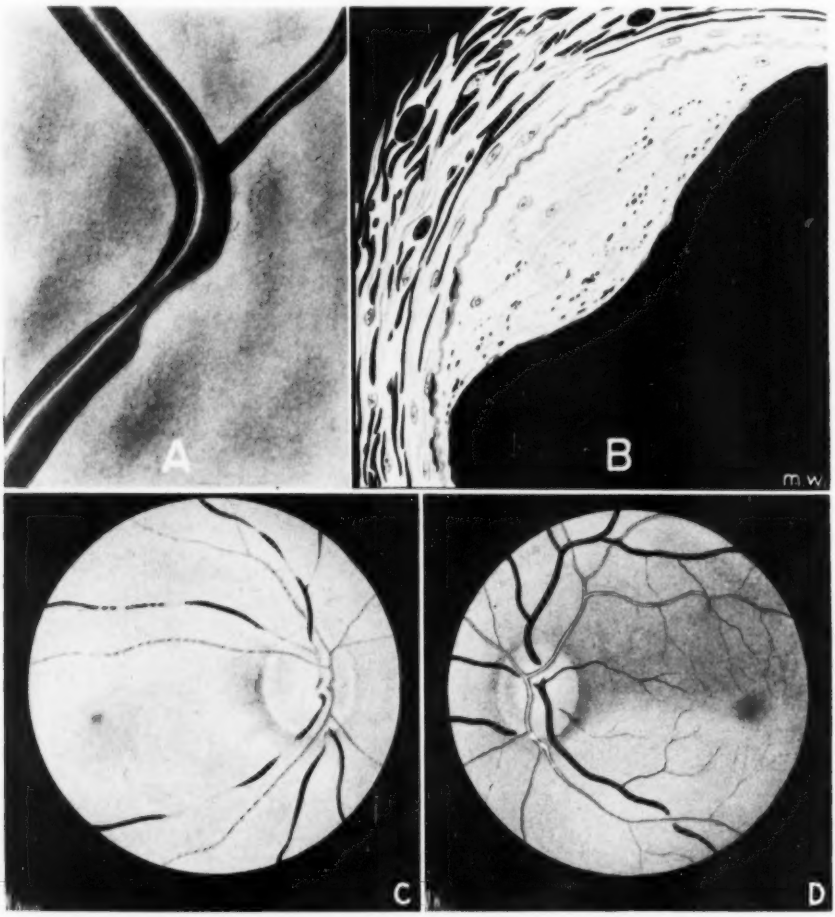

Fig. 5.—*A* and *B*, atheromatous plaque in retinal artery near disk: *A*, drawing showing indentation of arterial wall; *B*, schematic cross section of atheroma. *C*, occlusion of central retinal artery, showing pale edema of coagulation necrosis at posterior pole with cherry-red spot at macula; *D*, occlusion of branch of central retinal artery, showing pale edema of coagulation necrosis along distribution of obstructed artery.

Pathology.—The primary lesions, or atheromata, appear as small yellow round elevated linear areas of intimal thickening. Microscopically, they begin as localized areas of edema in which there is proliferation of connective tissue, cells, and fibers containing cholesterol crystals and lipid droplets, these substances accounting for the yellow color. Small lesions may coalesce to form larger ones (Fig. 4). As the

lesion becomes older, hyaline degeneration occurs, more lipid is deposited, and necrosis with ulceration may take place. Calcification of the hyaline and necrotic tissue may occur, with the formation of large calcified plaques in the intima.

Course.—The course of atherosclerosis is characterized by sudden vascular accidents, as exemplified by coronary occlusion, cerebral thrombosis, or hemorrhage. In smaller vessels, such as the coronary, the lumen may become narrow, and thrombosis, due to a proliferated endothelial mass or an associated thrombosis, with or without accompanying spasm may occur, or the wall may become thin and the rupture of the vessel take place.

Etiology.—The cause of atherosclerosis is unknown. Age and heredity are important, and its incidence is known to be somewhat increased in hypertension. Present thought indicates that a disturbance of lipid metabolism is at fault. Although atherosclerosis can be produced in the rabbit and the dog by feeding it large amounts of cholesterol or cholesterol and thiouracil, Keys and associates [5] have shown that there is no definite correlation between dietary cholesterol intake and serum cholesterol levels. More recently, Gofman and others [6] have suggested that the size and physical state of lipid molecules may be of greater importance in atherosclerosis than the serum level of cholesterol. Gofman and co-workers,[6] by the ultracentrifugal flotation of serum cholesterol and other serum lipids, classified molecules into four groups according to the rate (Sf units) at which they migrate in the flotation procedure. The group which they termed "Sf 10-20" seemed to be related to human atherosclerosis. These molecules were present in greater incidence in patients who had had myocardial infarction than in a supposedly normal group. Considerable debate has raged about these ideas, however, and a great deal of work is at present being carried out.

Distribution.—The lesions of atherosclerosis occur in a spotty manner throughout the body. The intensity varies from one portion of the body to another, so that the arteries of the brain, the heart, or the eye may be extensively involved, with little or no change occurring in the others. Because of this inconstant distribution and the difficulty of making an ophthalmoscopic diagnosis, ophthalmoscopic examination is not of great help in the management of this disease.

Ophthalmoscopic Signs of Intimal Atherosclerosis: The ophthalmoscopic diagnosis of intimal atherosclerosis is difficult because the main lesion occurs in the central retinal artery within the substance of the optic nerve at the level of the lamina cribrosa, as indicated by Friedenwald.[3] Manifestations of initial atherosclerosis as seen ophthalmoscopically are noted in the following tabulation (after Friedenwald [3]):

1. Atheromata at lamina cribrosa invisible
   (*a*) Narrowing of arterial tree
   (*b*) Increased number of branches at disk border
2. Lesions at or near disk serving as outposts of main lesions
   (*a*) Localized irregularity of blood column
   (*b*) White or opaque area in wall of vessel
3. Vascular accidents

5. Keys, A.; Mickelsen, O.; Miller, E. V. O., and Chapman, C. B.: Relation in Man Between Cholesterol Levels in the Diet and in the Blood, Science **112**:79, 1950.

6. Gofman, J. W., and others: Blood Lipids and Human Atherosclerosis, Circulation **2**:161, 1950.

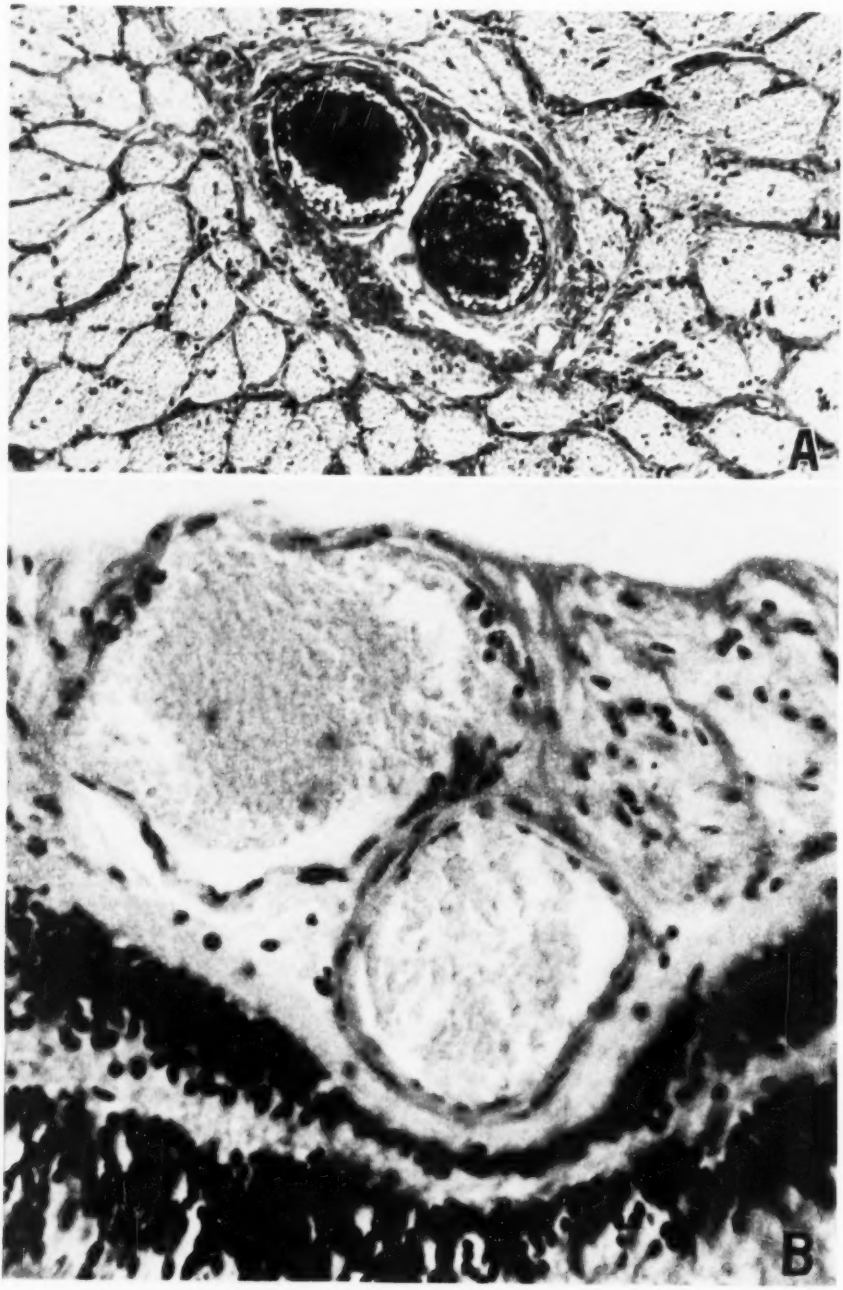

Fig. 6.—Sections showing common adventitial coat of (*A*) central artery and vein within optic nerve; (*B*) retinal artery and vein at arteriovenous crossing. Endothelial wall of vein rests on media of artery.

He stated that atheromata could occur in the retinal arteries peripheral to the lamina as far as the first or second bifurcation from the disk, but he believed that these were outposts of a more fully developed lesion upstream in the central artery at

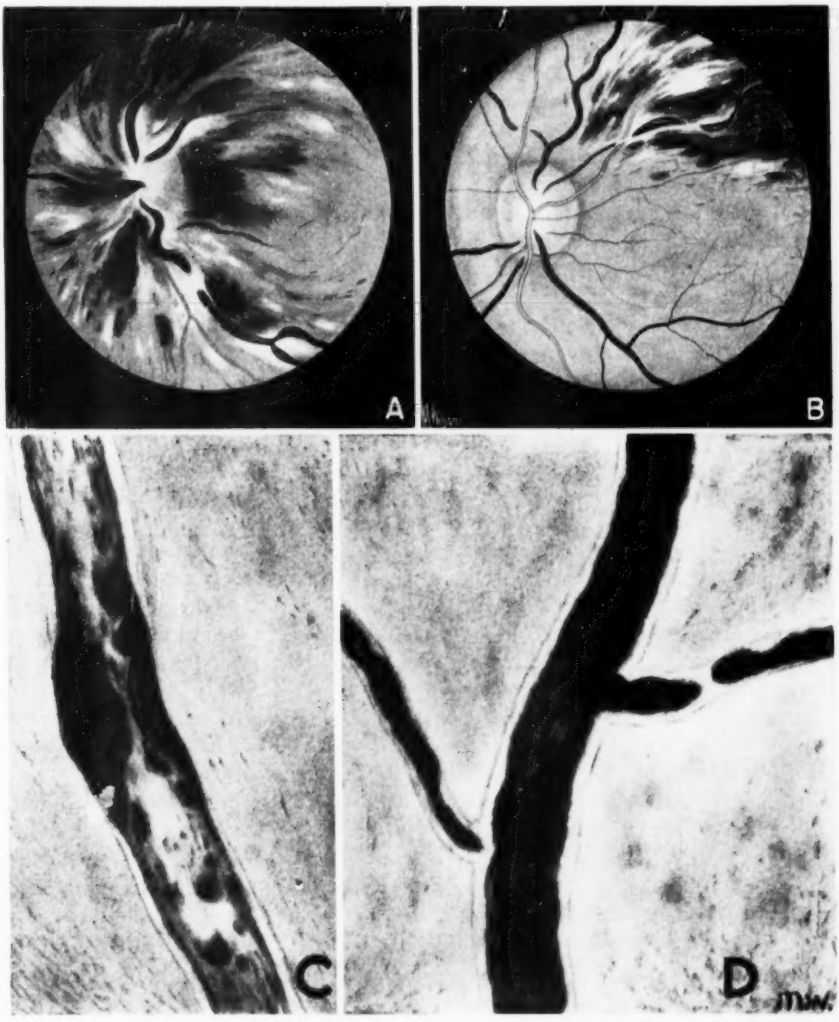

Fig. 7.—*A*, occlusion of central retinal vein; *B*, occlusion of branch of central retinal vein; *C* and *D*, flat preparations (fat stain) showing (*C*) intimal atherosclerosis and (*B*) arteriosclerosis in retinal arterial system (after Friedenwald[3]).

the level of the scleral foramen. The lesions in the retinal arteries produce minimal ophthalmoscopic changes and usually pass unrecognized.

The ophthalmoscopic diagnosis of intimal atherosclerosis is usually made by inference, rather than by seeing the lesion itself. Friedenwald[3] stated that fibrosis

of the atheroma in the central artery may, by contraction, shorten the artery and displace the retinal arteries toward the disk. He found that as the bifurcations are drawn onto the disk more vessels are seen to cross the disk margin. The retinal arteries also become straighter and bifurcations occur at more acute angles. An atheroma may encroach directly upon the lumen of the vessel or narrow the lumen by fibrosis. Marked diminution in blood flow results, with narrowing of the caliber of the retinal arterial tree.

The lesions occurring in the branches of the retinal artery near the disk may cause visible changes, but even these may easily be overlooked. They appear as localized constrictions in caliber indentation of the blood column by the atheromatous plaques which project into the lumen of the artery (Fig. 5*A* and *B*). Occasionally, the atheroma may appear as a whitish or opaque area in the wall of the vessel if fibrosis has occurred. In the eye, as elsewhere in the body, intimal atherosclerosis frequently manifests itself by vascular accidents. Thrombosis of the central retinal artery or one of its branches is a fairly frequent occurrence. A pale area of coagulation necrosis occurs along the distribution of the occluded vessels if only a branch is involved and the blood column of the obstructed vessel is markedly attenuated (Fig. 5*C* and *D*). If the central artery is occluded, a characteristic cherry-red spot develops in the macula, which is surrounded by extensive pale coagulation necrosis. The entire arterial tree is then markedly attenuated.

The eye is one site in the body where thrombosis of a vein occurs as a result of intimal atherosclerosis. This happens because the central retinal artery and vein, and the branches of the retinal artery and vein, are intimately associated at their arteriovenous crossings, where they share a common adventitial coat and the endothelial wall of the vein rests directly upon the media of the artery (Fig. 6). Atheromatous processes, therefore, may readily invade the wall of the vein, causing a similar atheromatous plaque in that vessel. Obstruction of the vein may occur at the point of such an atheroma as a result of proliferation of the plaque or of thrombus formation on the plaque. Constriction of the adventitial coat may contribute to the occlusion by compressing the vein against the more rigid arterial wall. The vein, therefore, may become obstructed, although the artery remains patent. This occurs oftenest at the level of the lamina cribrosa of the sclera, although obstruction of retinal veins at arteriovenous crossings is a rather common event (Fig. 7*A* and *B*). Because the atherosclerotic process is difficult or impossible to see, whether in the retinal branches or within the central vessels, the diagnosis often remains unsuspected until occlusion of one of these vessels occurs.

ARTERIOLAR SCEROSIS AND HYPERTENSION

Mechanism.—Arteriolar sclerosis is an entirely different disease from intimal atherosclerosis, as was also pointed out by Friedenwald.[3] It is caused by hypertension, and its changes represent damage to the arterioles from the stress and strain of elevated blood pressure. The vessel walls show diffuse involvement, rather than the spotty, plaque-like lesions of intimal atherosclerosis (Fig. 7*C* and *D*). Hyaline material, often with considerable lipid, first is deposited just outside the endothelium. As the disease progresses, the muscularis becomes involved, and finally the entire thickness of the vessel wall. The arteriole becomes rigid, and contractile power is diminished or lost. Arteriolar sclerosis is a generalized disease which involves the

arterioles throughout the body very uniformly. This is of especial importance because the characteristic changes which it produces in the retinal arterioles probably reflect fairly accurately those which have occurred elsewhere in the body, for example, in the arterioles of the kidney (Fig. 8).

The ophthalmoscopic changes of hypertension usually precede those of arteriolar sclerosis, and they will therefore be described in that order. The exact cause of hypertension is still somewhat obscure, but there is considerable agreement that the mechanism of the elevated intra-arterial pressure is an increase in peripheral resistance to blood flow which results from generalized constriction of the arteriolar bed throughout the body. Whether the arteriolar constriction is on a neurogenic, humoral, or other basis has not definitely been established in all instances. Early in the hypertensive state the peripheral arterioles show normal physiological responses to physical and chemical stimuli, evidence that the disturbance is functional. The ophthalmoscopic changes seen in the retinal arterioles in hypertension support such a hypothesis.

Ophthalmoscopic Changes of Hypertension.—All the ophthalmoscopic changes of hypertension can be explained readily on the basis of constriction of arterioles.

1. Narrowing of the Retinal Arterioles: The earliest fundus change is attenuation of the retinal arterioles. These changes are best observed in toxemia of pregnancy or in cases of hypertension of rapid onset in young persons in which the duration has been insufficient for organic damage (arteriolar sclerosis) to develop. Narrowing or attenuation of the retinal arterioles is usually proportional to the degree of elevation of blood pressure. If the hypertension is very mild, ophthalmoscopically visible arteriolar constriction may or may not be present, whereas if severe, it may be pronounced. Minimal narrowing of the vessels is most easily seen in the smaller branches of the arterial tree beyond the first or second bifurcation.

2. Irregularity in Caliber: In severer hypertensive states irregularities in the caliber of blood vessels, thought to be due to localized spasm and contraction of the wall of the arteriole, may be superimposed upon generalized narrowing. The narrowing and irregularity may increase until the vessels become thread-like.

3. Hemorrhages: In very severe hypertensive processes in which the arteriolar spasm and narrowing are extreme, blood flow through the capillaries may be so impaired that nutritional damage to the capillary walls and tissues of the retina may result. Blood cells may escape through the damaged walls, thus explaining the appearance of retinal hemorrhages.

4. Exudates: Exudates of two types may occur during hypertensive states. They probably result from nutritional disturbances secondary to severe arteriolar spasm.

(a) Cotton-wool exudates. Localized degeneration of the retina, called ganglioform degeneration, or possibly accumulations of fibrin, may give the appearance of fluffy cotton-wool exudates. This type of exudate is characteristically seen during acute phases of severe hypertension.

(b) Hard, shiny exudates. If the severe hypertensive phase continues over a sufficiently long time, lipid degeneration and infiltration of the retina occur and are seen as hard, shiny-white exudates in the macular region, often in the form of a star. Histologically, these represent lipid deposits in the deep layers of the retina.

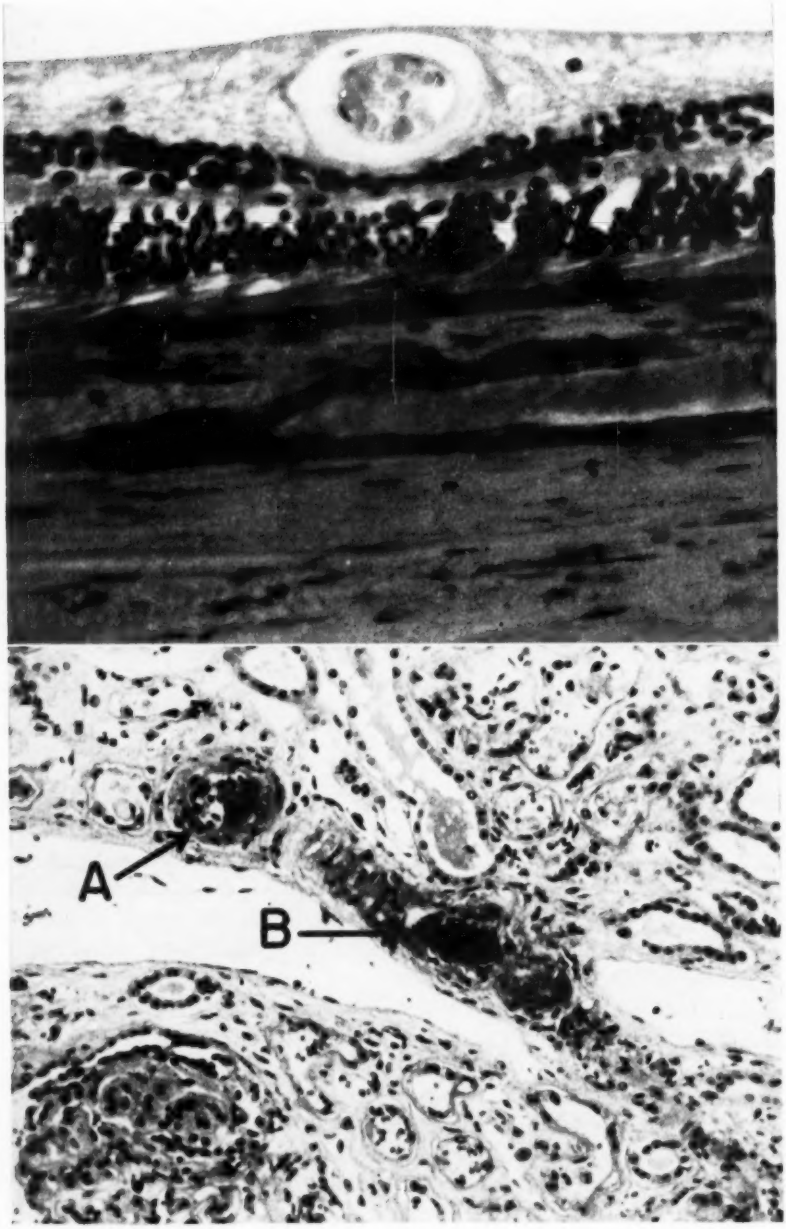

Fig. 8.—Above, arteriolar sclerosis involving retinal arteriole; below, arteriolar sclerosis involving renal arterioles, in (*A*) cross section and (*B*) sagittal section.

5. Edema of Disk and Retina: In the severest hypertensive states papilledema occurs, usually on a local circulatory basis. Less frequently it may result from hypertensive encephalopathy.

6. Arteriolar Sclerosis: If the hypertension continues for a sufficiently long period, the changes of arteriolar sclerosis develop in the walls of the arterioles. Arteriolar sclerosis appears more rapidly in severe than in mild hypertensive states. However, if a mild hypertension continues for a long time, arteriolar sclerosis may be pronounced. One might expect, therefore, to find any degree of hypertensive change combined with almost any degree of change of arteriolar sclerosis, depending upon the severity and duration of the hypertension.

Because retinal changes of hypertension stem from narrowing of the retinal arterioles, ophthalmoscopic examination is of little aid in determining the cause of the hypertensive process. The ophthalmoscopic signs of hypertension associated with chronic glomerulonephritis may differ in no way from those of malignant hypertension. Although, as pointed out by Wagener,[2] the retinitis of nephritis often shows more marked exudative phenomena, pallor of the disk, due to anemia, less narrowing of the arterioles, and less arteriolar sclerosis, this by no means is invariable.

Ophthalmoscopic Changes of Arteriolar Sclerosis.—The ophthalmoscopic signs of arteriolar sclerosis reflect changes in the appearance of the blood column due to thickening of the wall of the arteriole. Normally, the retinal arterioles appear a clear pink, and a small central reflex of light appears along the wall. This light streak is formed by the reflection of the light from the convex cylindrical surfaces of the blood column, and the surrounding vessel walls, which are relatively transparent. The light streak in the arteries is always wider and brighter than that of veins of similar caliber. As suggested by Friedenwald,[3] the outer surface of the muscle coat must therefore contribute an important factor to the light streak, and, similarly, any changes in the thickness of the coat of the wall of the vessel with an associated increase in its refractive index should cause an increase in the width and brightness of the arterial light streak.

1. Changes in the Light Streak: Among the earliest changes to occur are alteration in the reflection from the wall of the arterioles and the appearance of the blood column.

(a) Widening of the light streak. The first change of arteriolar sclerosis is widening of the arteriolar light streak.

(b) Copper-wire arteries. As the light streak increases in width, it eventually becomes so broad that it occupies most of the surface of the vessel. The vessel then has the appearance of burnished copper, hence the term "copper-wire," a sign first described by Gunn in 1898.

(c) Silver-wire arteries. In the extreme form of arteriolar sclerosis the vessel wall is so thickened, as a result of hyalinization and lipid infiltration, that the vessel wall obscures the blood column. The artery then appears as a white cord, even though blood is still circulating through it.

2. Changes in Arteriovenous Crossings (Fig. 9): Many different signs have been described at the arteriovenous crossings as indicating the pressure of arteriolar sclerosis. They result from thickening of the wall of the arteriole and associated changes in the veins at the arteriovenous crossings. The commonest appearance is

that of compression of the vein by the artery. This may vary in severity from the slightest indentation to nearly complete interruption of the vein where the artery crosses (Fig. 9*B*).

(a) Tapering of vein. Occasionally, if the sclerotic process in the artery extends to the adventitia of the vein, the column of blood in the vein will be partially obscured and appear tapered on each side of the arteriovenous crossing, the so-called tapering of the veins (Fig. 9*E*).

(b) Banking of vein. Occasionally, owing to constriction or compression of the veins, the blood return may be impeded and the veins become distended for some distance peripheral to the crossing. This has been called Gunn's sign, and has also been referred to as "banking" (Fig. 9*F*).

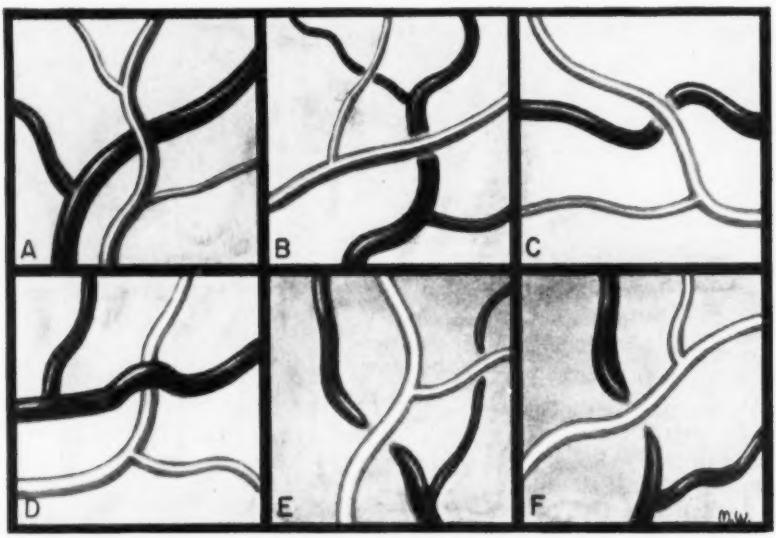

Fig. 9.—Changes in arteriovenous crossing in arteriolar sclerosis: (*A*) normal crossing; (*B*) early arteriovenous compression; (*C*) deviation of vein; (*D*) humping of vein; (*E*) tapering of vein; (*F*) banking of vein.

(c) Deflection of vein. Deflection of a vein from its normal course is a common appearance at the point where the artery crosses. The vein may dip down into the retinal tissues if the artery passes over the vein, or, if the reverse is true, the vein may assume the appearance of an arch or hump over the artery, owing to vertical deflection, a change which has been referred to as the "Salus sign" (Fig. 9*D*). Lateral deflections are even commoner. Instead of crossing the artery obliquely, the vein does so at right angles and appears S-shaped at the bend (Fig. 9*C*). Likewise, if the artery shortens through contraction, or lengthens, the veins are displaced at their crossing.

3. Tortuosity of Vessels: The arteries may increase in length, as well as thickness, and as a result become increasingly tortuous. This is best seen in the small

arterioles of the macular region and was first described by de Schweinitz in 1906. Hemorrhages and exudates ordinarily do not occur with arteriolar sclerosis or atherosclerosis unless due to branch obstruction of one of the retinal vessels or unless the hypertensive changes are severe.

A SYSTEM FOR GRADING THE OPHTHALMOSCOPIC CHANGES OF HYPERTENSION AND ARTERIOLAR SCLEROSIS

The retinal changes of hypertension and arteriolar sclerosis should be graded separately because of their different significance. The ophthalmoscopic changes of hypertension (i. e., the narrowing and irregularity of the retinal arterioles and the presence of associated nutritional changes, which may include retinal hemorrhages, exudates, and edema of the disk and retina) result from vasospasm, and their severity, therefore, must parallel the intensity of the vasospastic element of the hypertensive process.

The changes of arteriolar sclerosis, on the other hand, furnish an estimate of the damage to the arterioles due to the wear and tear of elevated intra-arterial pressure. Evaluation of the severity of the sclerosis of the retinal arterioles, therefore, is probably of greater value to the internist than an estimate of the hypertensive state. The severity of hypertension can readily be assessed by blood pressure measurements and other means, but the degree of sclerosis may be very difficult to determine. Furthermore, the amount of sclerosis serves as an excellent index to the duration of the hypertension. Minimal or no sclerosis suggests recent origin of the hypertension, particularly if the hypertension is severe. Marked sclerosis indicates longer duration, although it develops more rapidly with severe than with mild hypertension. This is of importance because, although the diagnosis and severity of hypertension can be determined by the internist with great accuracy, the duration is often difficult to ascertain. The history is notoriously unreliable. Quantitative evaluation of the degree of sclerosis seems of increasing value with the development of more effective means of lowering blood pressure. It would seem advantageous to inform the internist about the severity of the arteriolar sclerosis, because if none were present, the hypertension would have caused little organic vascular change, while if severe the damage would be marked and the prognosis poorer. Better response to surgical treatment would be expected in a patient with mild than in one with severe sclerosis.

Wagener and associates [2] introduced a system of grading hypertensive arteriolar sclerosis which has been of great value, but it embodies interpretations which are difficult for the average ophthalmologist and internist to use in everyday practice. Wagener's method, however, has proved to be of great value in the management of hypertension, particularly in the selection of patients for various types of hypertensive surgery, as advocated by Smithwick [7] and others. A more or less similar method of grading was advocated by a committee of the American Ophthalmological Society [8] for the classification of hypertension, of which Wagener was a member.

7. Smithwick, R. H.: Hypertensive Cardiovascular Disease: Effect of Thoracolumbar Splanchnicectomy on Mortality and Survival Rates, J. A. M. A. **147**:1611, 1951.

8. Wagener, H. P.; Clay, G. E., and Gipner, J. R.: Retina in the Presence of Vascular Hypertension, report submitted to the American Ophthalmological Society by the Committee on Classification of Hypertensive Disease of the Retina, 1946.

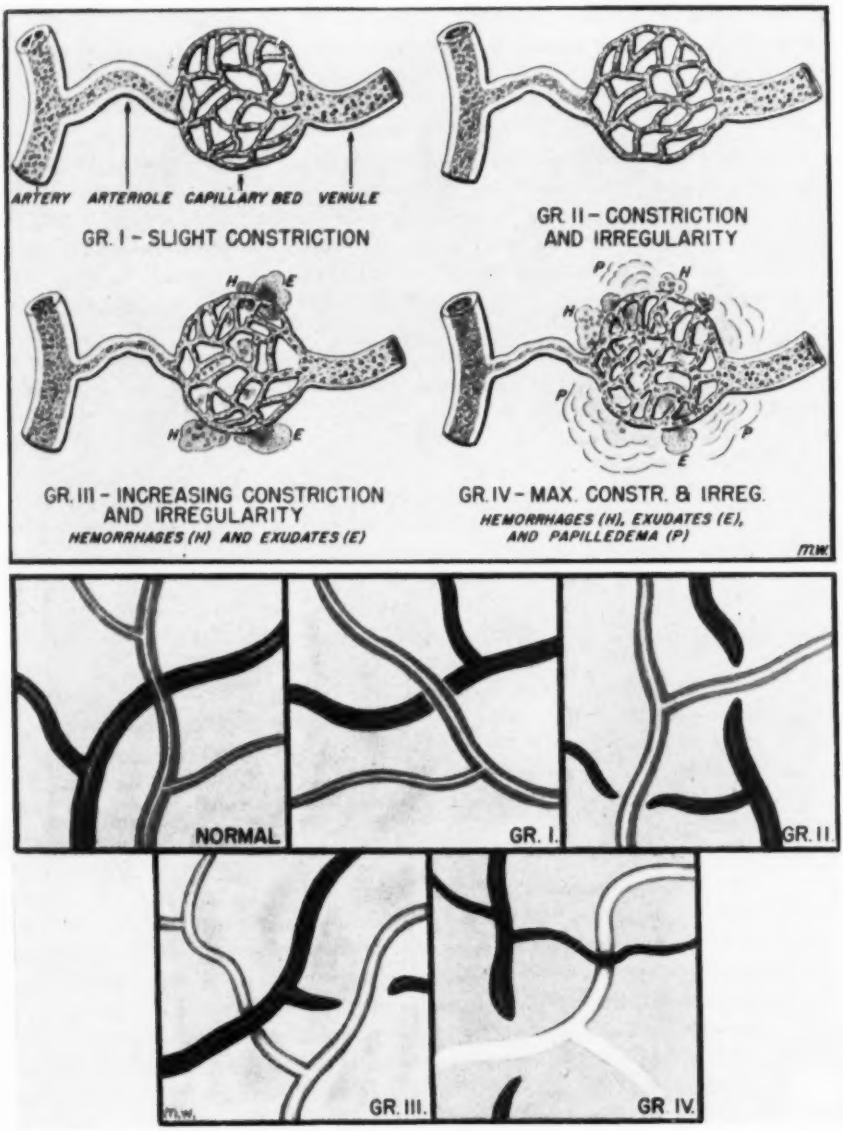

Fig. 10.—Above, schema for ophthalmoscopic classification of hypertension; below, schema for ophthalmoscopic classification of arteriolar sclerosis.

This committee suggested grading the narrowing, the focal spasm, and the sclerosis of the retinal arterioles separately in Grades I to IV. The advisability of grading the first two types of change separately is questionable, since they are both manifestations of hypertensive change.

A simplified system for the separate grading of the retinal changes of hypertension and arteriosclerosis is suggested which includes narrowing and focal spasm in the category of hypertensive changes and utilizes criteria which are rather easy to recognize and to duplicate. It permits considerable uniformity in grading by different observers using the same system. The concepts used to establish this system have been well sustained over a period of five years in the observation of a large number of patients with hypertension.

The hypertensive changes are graded from normal to IV (Fig. 10, above). Many patients with mild hypertension have so little narrowing of the retinal arterioles that the vessels must be termed normal. When the hypertension is severer, arteriolar narrowing may be recognizable, particularly in the secondary branches, and the changes are termed Grade I. Minimal changes, such as these, would often

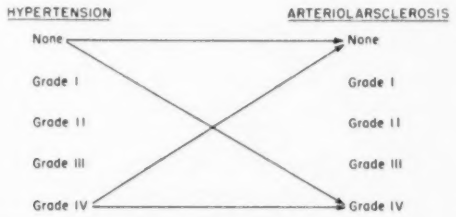

Fig. 11.—Correlation of degree of retinal changes of hypertension and degree of retinal arteriolar sclerosis.

be overlooked if the patient had not been referred with the diagnosis of hypertension. Grade II hypertensive changes are said to exist when the narrowing is still more pronounced and localized irregularities, indicating severer spasm, are present. Grade III hypertensive changes consist of still more extreme narrowing and irregularity of the retinal arterioles, accompanied by retinal hemorrhages or exudates or both. Wagener [2] insists upon the presence of retinal exudates in permitting the designation of Grade III, but if care is taken to exclude branch thrombosis of a vessel and if the severity of the arteriolar constriction is compatible the designation of Grade III at times might be justifiable on the basis of the presence of scattered hemorrhages alone. The decision, however, is at best an arbitrary one, and for purposes of uniformity the presence of exudates should be relied upon. Grade IV hypertensive changes consist of all the signs characteristic of Grade III plus papilledema.

The changes of arteriolar sclerosis are graded on the basis of alteration of the light reflex from the arterioles and arteriovenous-compression phenomena. Many patients with hypertension show no evidence of sclerosis and must be classed as such, or Grade 0 (Fig. 10, below). The earliest recognizable increase in light reflex associated with minimal arteriovenous compression is termed Grade I. These changes, when more marked, are termed Grade II. The presence of copper-wire arteries and still more marked arteriovenous compression make up Grade III. Silver-wire arteries indicate the severest degree of sclerosis, or Grade IV.

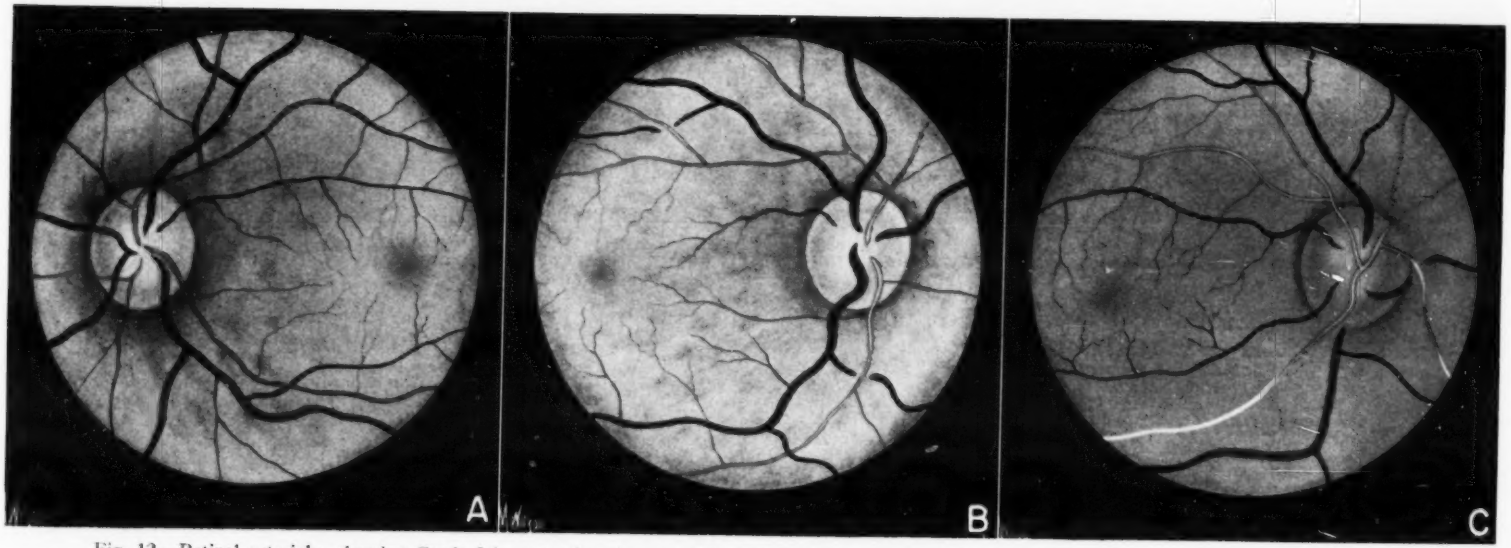

Fig. 12.—Retinal arterioles showing Grade I hypertensive changes with (*A*) Grade I sclerosis, (*B*) Grade III sclerosis, and (*C*) Grade IV sclerosis.

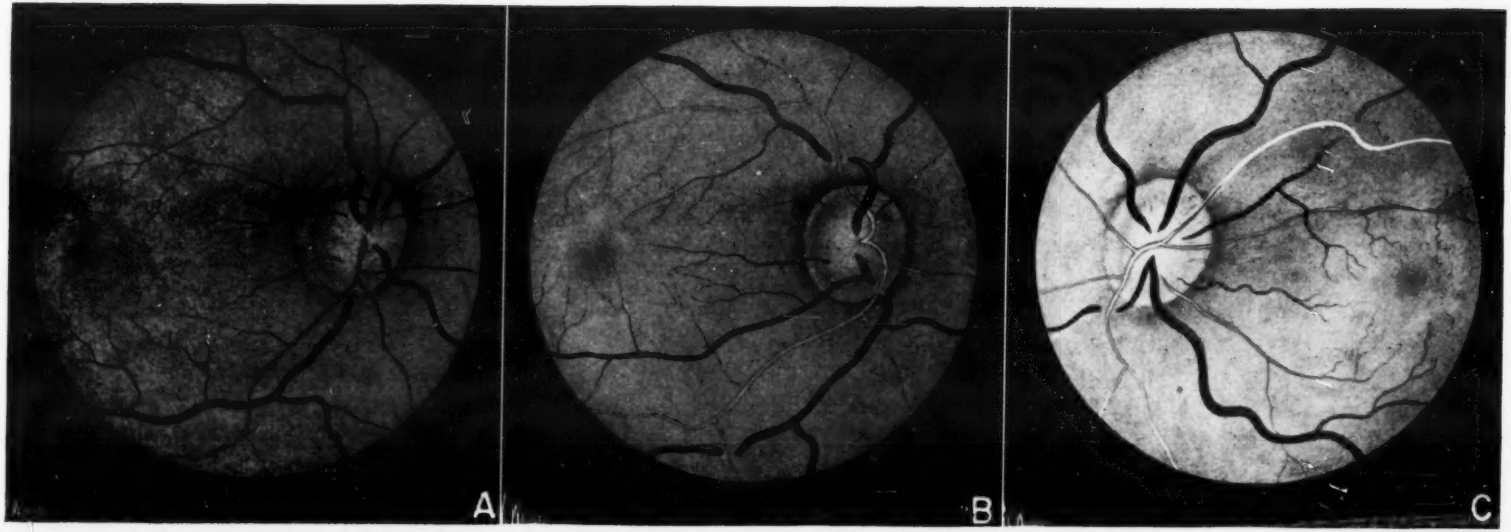

Fig. 13.—Retinal arterioles showing Grade II hypertensive changes with (*A*) Grade I sclerosis, (*B*) Grade III sclerosis, and (*C*) Grade IV sclerosis.

Fig. 14.—Retinal arterioles showing Grade III hypertensive changes with (*A*) Grade O sclerosis, (*B*) Grade II sclerosis, and (*C*) Grade IV sclerosis.

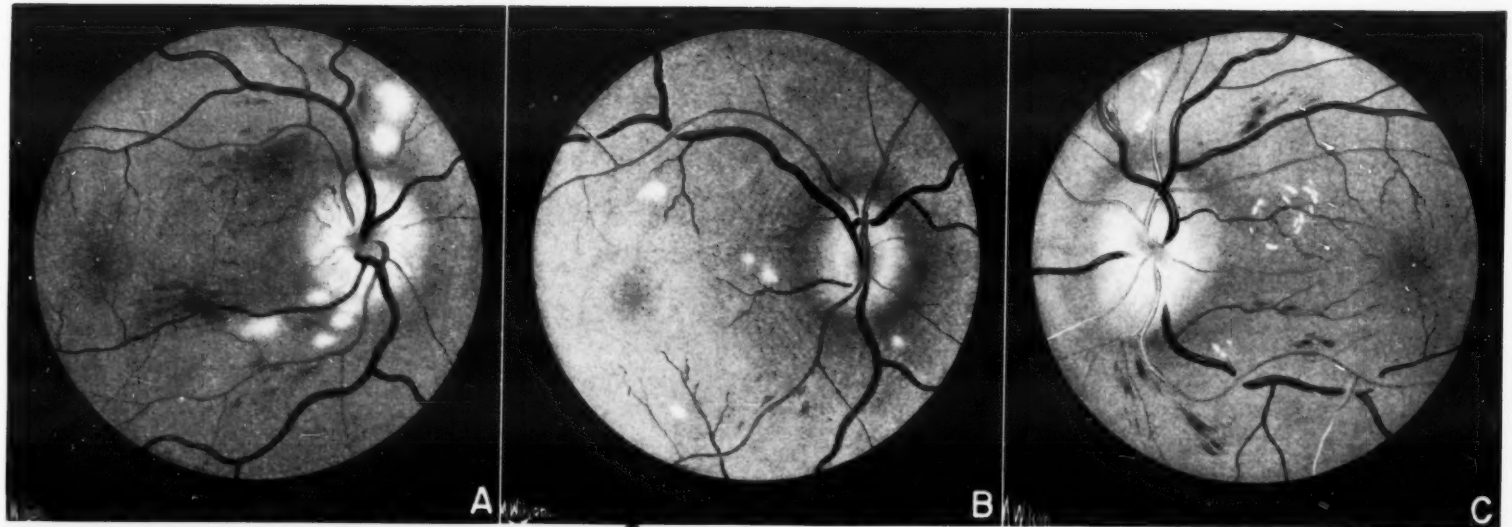

Fig. 15.—Retinal arterioles showing Grade IV hypertensive changes with (*A*) Grade O sclerosis, (*B*) Grade II sclerosis, and (*C*) Grade IV sclerosis.

Any degree of arteriolar sclerosis might conceivably occur with any degree of hypertensive change (Fig. 11). A mild hypertension might cause marked changes of arteriolar sclerosis over a period of years, while an acute fulminating malignant hypertension might go on to terminate with almost no sclerosis. On the other hand, a malignant hypertension could be accompanied by Grade IV retinal arteriolar sclerosis if the disease were superimposed upon a long-standing benign hypertension. Considerable information is therefore gained regarding the severity of the hypertension at the time of examination, the duration of the process, and, at times, the prognosis.

SUMMARY

1. The anatomical characteristics of the retinal arterial tree are reviewed.

2. The various types of arteriosclerosis are enumerated. Emphasis is placed on differentiating between sclerosis, athero- and arteriolar sclerosis, the two types which can occur in the retinal arterioles.

3. The ophthalmoscopic signs of hypertension and arteriolar sclerosis are listed.

4. A system of grading the severity of the ophthalmoscopic changes of hypertension and arteriolar sclerosis is suggested. Each is graded separately because the hypertensive changes indicate severity of the hypertensive process and the changes of arteriosclerosis reflect organic damage to the arterioles by the wear and tear of hypertension.

Dr. William C. Frayer assisted in obtaining histologic material for the photomicrographs in this paper.

CHORIORETINITIS OF CONGENITAL SYPHILIS

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THE PURPOSE of this study is to determine the incidence of chorioretinitis in children with congenital syphilis, especially with interstitial keratitis; to compare our findings with the well-known classification of Sidler-Huguenin; to discuss the frequency and diagnostic significance of perivasculitis in the eyegrounds of patients with congenital syphilis, points which we believe have not been sufficiently stressed, and to discuss the differential diagnosis of the retinitis pigmentosa type of syphilitic chorioretinitis and primary pigmentary degeneration of the retina.

Although the incidence of congenital syphilis in the United States is decreasing and a syphilitic infant is rapidly becoming an anachronism,[1] chorioretinitis of congenital syphilis is still of importance, considering that in its atrophic stage it exists throughout the patient's life. Its diagnostic importance becomes apparent. The younger generation of ophthalmologists have less opportunity of seeing chorioretinitis of congenital syphilis, and, in contrast to the older literature, many modern texts do not, we believe, afford a comprehensive discussion of the disease.

It is of interest that in congenital syphilis the choroid and cornea are most susceptible to syphilitic involvement, its frequency being comparable to that of the osseous system, whereas in acquired syphilis the iris is more susceptible, the choroid is considerably less so, and the cornea is rarely involved.[2]

REVIEW OF LITERATURE

Sidler-Huguenin credited Baeder, in 1858, with being the first to describe chorioretinal changes of congenital syphilis. He described such changes in a patient after the disappearance of interstitial keratitis.

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1. This statement does necessarily apply to the incidence of congenital syphilis throughout the world. For example, according to Wolf (Der ärztliche Standpunkt in der Frage der Heiratserlaubnis, Ztschr. Haut u. Geschlechtskr. **11**:156, 1951), 0.3% of children in Hamburg under one year of age have congenital syphilis.

2. We are skeptical of the occurrence of interstitial keratitis in acquired syphilis. The notable, if not the only, syphilitic involvement of the cornea in acquired syphilis is keratitis pustuliformis profunda.

Subsequent to Baeder's publication a number of reports of chorioretinitis of congenital syphilis appeared in which a limited number of patients were studied and no attempt was made at classification or separation of the condition from the eyeground changes of acquired syphilis. Mention may be made of the reports of Hutchinson [3] (1863), Bull [4] (1884), Nettleship [5] (1886), Ohanian [6] (1894), and Silex [7] (1896), and more especially of Haab [8] (1895) and Hirschberg [9] (1900), who separated the different forms of chorioretinal changes of congenital syphilis.

Sidler-Huguenin's Classification.—The classification of the chorioretinal changes in congenital syphilis was consummated in the exhaustive study of Sidler-Huguenin [10] in 1904. He reported in detail the eyeground changes of 125 patients with congenital syphilis. Despite the shortcomings of his classification, his contribution can still be regarded as one of the monumental contributions to ocular syphilis.

Type 1 (Fig. 1): This is the much-quoted "salt-and-pepper" fundus, appearing like salt and pepper sprinkled on a yellowish-red background. He regarded the process as essentially a retinitis. It is presented as many fine, roundish, yellowish-red dots, intermingled with similarly fine brown or black pigmented dots. The process is most frequently confined to the periphery and is invariably bilateral; at times the disease extends to the posterior pole, and only single quadrants may be affected. Vision is usually unimpaired; the macula is uninvolved, and the optic disk is normal in color. The disease is nonprogressive. In the patients that he observed over a period of years no change in the disease occurred.

In not very characteristic cases it may be difficult to decide whether there is pathologic alteration or the normal speckling seen in blind children.

Sidler-Huguenin described mild, moderate, and severe forms of the disease. In the moderate and severe types, the retinal vessels are narrowed, although pronounced vascular changes are rare; the optic nerve is pale, and there is alteration in vision and in the perimetric fields. In the severe form of the disease the pigmented lesions become larger and assume various shapes, simulating the picture of retinitis pigmentosa. Type 1 was observed in 30 of his 125 patients. Of these 30 patients, 6 were below the age of 14 months; the youngest was 7 weeks old.

Type 2 (Fig. 2): This is seen as round or oval pigmented lesions, occurring singly or in groups. Through confluence the lesions become enlarged and assume variable shapes, at times having outgrowths or extensions. Intermingled with the pigmented lesions are yellowish-red lesions, which are fewer and have less tendency to become confluent. Areas of choroidal atrophy may be observed.

3. Hutchinson, J.: A Clinical Memoir of Certain Diseases of the Eye and Ear Consequent on Inherited Syphilis, London, J. Churchill, 1863, pp. 130-150.

4. Bull, O.: The Ophthalmoscope and Lues, Christiana, P. T. Mulling, 1884.

5. Nettleship, E.: On the Pathological Changes in Syphilitic Choroiditis and Retinitis, Ophth. Hosp. Rep. London, **11**:1, 1886.

6. Ohanian, C.: Contribution à l'étude des affections hérédo-syphilitiques de l'œil, Thesis, Geneva, 1894.

7. Silex, P.: Pathognomische Kennzeichen der congenitalen Lues, Berl. klin. Wchnschr. **33**:139, 1896.

8. Haab, O.: An Atlas of Ophthalmoscopy, with Introduction to Use of the Ophthalmoscope, translated and edited by E. Clark, London, Baillière, Tindall & Cox, 1895.

9. Hirschberg, J.: Diskussion über die Augenhintergrundsveränderungen bei Heredosyphilis, Transactions of Thirteenth International Medical Congress, Paris, 1900; Über Entzündung der Netzhaut und des Sehnerven in Folge von angeborener Lues, Deutsche med. Wchnschr. **32**:746, 1906.

10. Sidler-Huguenin: Über die hereditär-syphilitischen Augenhintergrundsveränderungen, nebst einigen allgemeinen Bemerkungen über Augenkrankungen bei angeborener Lues, Beitr. Augenh. **51**:1, 1904.

The disease is situated primarily in the choroid and may be confined to the periphery or to small segments in the periphery. The disease may extend to the equator or the posterior pole. In this event the greatest alteration occurs at the periphery.

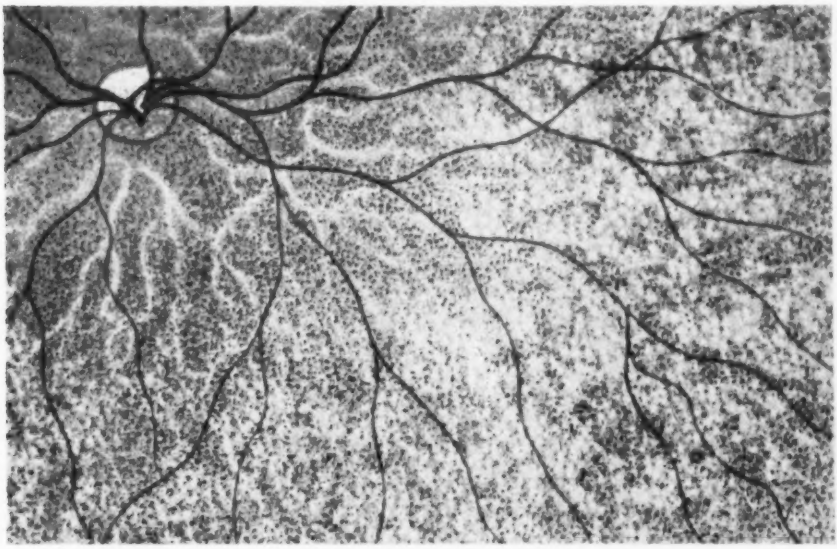

Fig. 1.—Mild form of Type 1. Reproduced from Sidler-Huguenin.[10]

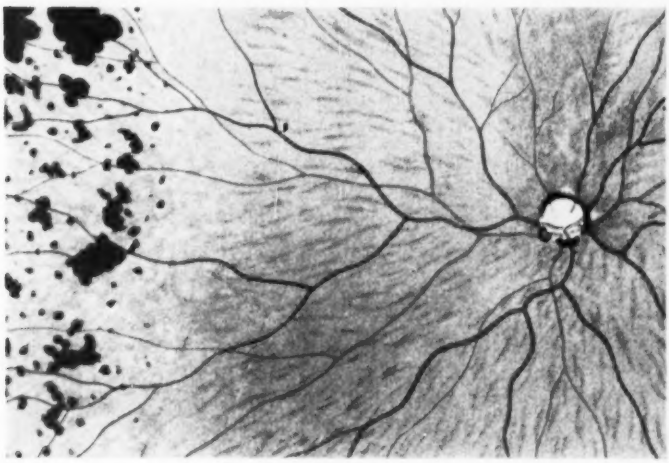

Fig. 2.—Type 2. Reproduced from Fig. 41 in Haab's "Atlas".[5]

Type 2 is usually bilateral (in 41 of Sidler-Huguenin's 47 cases), but, in contrast to Type 1, it may occur unilaterally. Sidler-Huguenin regarded this type as in some way associated with interstitial keratitis, since it is frequently observed before or after that disease.

Visual acuity and perimetric fields are usually unaffected except in instances in which the disease extends over the fundus. Sidler-Huguenin regarded the prognosis as good, since the process remains stationary and, in contrast to severe forms of Type 1, shows no tendency to pigment degeneration. He observed Type 2 in 47 of 125 patients.

Type 2 may be combined with what Silex called choroiditis areolaris—a rounded, light lesion, which is partially or completely ringed with pigment and in which there are rounded central pigmented lesions, or a pigmented lesion with a light center. These configurations assume the form of a "target" (*Schiesscheibenförmige Figur*). Silex regarded these lesions as characteristic of congenital syphilis.

Type 3 (Fig. 3): This occurs as small yellowish-red areas, which first appear in the periphery. The lesions remain small or coalesce, becoming larger and assuming various shapes. Prolongations extend toward the posterior pole.

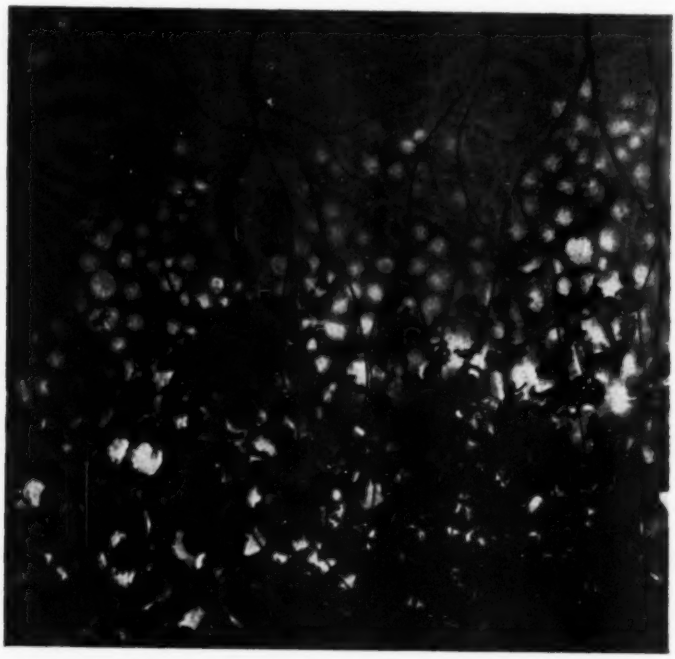

Fig. 3.—Late form of Type 3. Reproduced from Sidler-Huguenin.[10]

In some cases these light areas may remain unpigmented for many years, or throughout the patient's life. In other cases sooner or later the lesions become pigmented. Pigmentation first appears at the borders of the lesions and extends centrally. In later stages considerable pigmentation is presented.

Sidler-Huguenin was undecided whether the pathologic process primarily involved the choroid or the retina. At its onset he observed clouding of the vitreous, which later disappeared, and some opacities of the cornea.

Since the process predominantly affects the periphery, visual acuity and perimetric fields are generally unaffected. He regarded the prognosis as good. This type was observed in 18 of his 125 patients.

Type 4 (Fig. 4): On account of the resemblance of this type to primary pigmentary degeneration of the retina, it is often confused with that disease and has led to much controversy. Sidler-Huguenin regarded the process as primary in the retina, with secondary pigment degen-

eration. The peripapillary zone is dark-gray or bluish-gray, a feature which Sidler-Huguenin considered characteristic. The choroidal and retinal vessels are narrowed and sclerosed. Atrophy of the optic nerve invariably ensues; the disk becomes pale, but the margins are sharply demarcated. Complete atrophy in cases of pronounced progressiveness and in cases of long duration is rare.

Pigment alterations are presented as large pigmented plaques and in spots. The latter assume various configurations—round, oval, many-cornered, star-shaped, or resembling bone corpuscles. The many-cornered pigmented lesions have fine extensions which anastomose with neighboring lesions. These extensions do not appear, however, to connect with the retinal vessels. With the aforementioned lesions there are one to three papilla-sized pigmented plaques.

In addition, there occur yellowish-red lesions of chorioretinitis and pale lesions of choroiditis, which are usually round and show no tendency to coalesce. Rarely are these lesions absent or sparse.

The process is invariably bilateral and may be more pronounced either in the posterior pole or at the periphery.

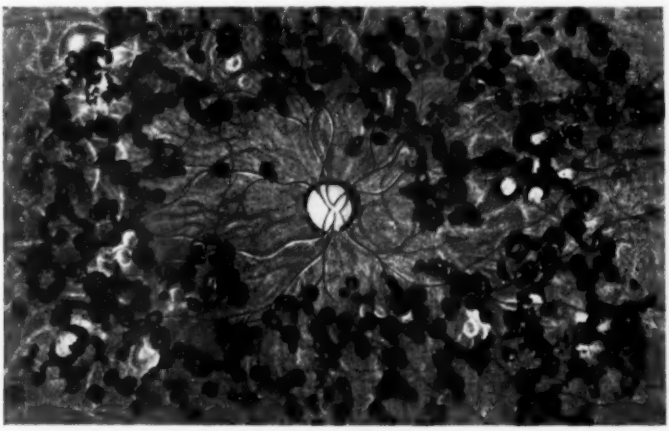

Fig. 4.—Type 4. Reproduced from Sidler-Huguenin.[10]

There is disturbance of visual acuity and of perimetric fields. The prognosis is unfavorable (more than in the other three types), in consideration of atrophy of the optic nerve and of extensive degeneration of the retina. However, it is better than that in primary pigmentary degeneration of the retina.

Sidler-Huguenin observed that no correlation could be made between the ophthalmoscopic picture and the degree of functional loss. Of his 125 cases, 21 were classified as of Type 4.

MIXED FORMS: In his series Sidler-Huguenin observed four patients who presented two types of the disease—Type 1 in conjunction with either Type 2 or Type 3. These patients had had interstitial keratitis. He assumed that the original type was Type 1 and that either before or after interstitial keratitis the other type of chorioretinitis developed.

He stated emphatically that he had never observed the transition of one type into another, or the disappearance of one type and the subsequent appearance in the same patient of another type.

Age at Onset.—Sidler-Huguenin [10] and Hirschberg [9] expressed the opinion that chorioretinitis is not rare in syphilitic infants. Schlimpert [11] observed patho-

11. Schlimpert, H.: Pathologisch-anatomische Befunden den Augen bei zwei Fällen von Lues congenita, Deutsche med. Wchnschr. **32**:1942, 1906.

logic alterations in the choroid of a 4-month syphilitic fetus. Friedenwald,[12] in his histologic study of the eyes of 175 syphilitic infants, found ample evidence of chorioretinitis attributable to syphilis. Igersheimer[13] observed transition from fresh chorioretinitis to the pigmented stage in infants examined in their first year of life and, again, in the second year. Other reports of its occurrence in infants, especially by Russian investigators, are discussed later.

Incidence Associated with Interstitial Keratitis.—The incidence in patients who have had interstitial keratitis varies considerably as reported by different writers. Thus, Clausen[14] and Herzau and Hossman[15] observed such changes in 5% and Pfister[16] in 7%, whereas Cunningham[17] observed it in 68% of his patients. Derby[18] gave its incidence as 55%. He stated that the process was most frequently seen as disseminated rounded lesions, usually situated in the equatorial region.

Anke[19] reported its incidence as 16%; Spicer[20] as 20%; Hoehne,[21] as 28%, and Igersheimer,[13] as 36%. In Klauder and Vandoren's[22] analysis of 532 case records of patients with interstitial keratitis, chorioretinitis was recorded in 7.9%.

Very few authors record the incidence of the disease in terms of Sidler-Huguenin's four types. In Dalsgaard-Nielsen's[23] study of 122 patients, Type 1 was observed in 1%, Type 2 in 14%, and Type 4 in 1%. Of 231 patients reported by Nordmann,[24] Type 1 was recorded in 13.3% and Type 2 in 15.5%. Oksala[25] observed Type 1 in 4.8% and Type 2 in 5.4%. Types 3 and 4 were not observed.

12. Friedenwald, J. S.: Ocular Lesions in Fetal Syphilis, Bull. Johns Hopkins Hosp. **46**:185, 1930; Tr. Am. Ophth. Soc. **27**:203, 1929.

13. Igersheimer, J.: Syphilis und Auge, in Jadassohn, J.: Handbuch der Haut- und Geschlechtskrankheiten, Berlin, Julius Springer, 1928, Vol. 17, pp. 244-255.

14. Clausen, W.: Aetiologische, experimentelle und therapeutische Beiträge zur Kenntnis der Keratitis interstitialis, von Graefes Arch. Ophth. **83**:399, 1912.

15. Herzau, W., and Hossman, E.: Über Keratitis parenchymatosa, Klin. Monatsbl. Augenh. **88**:464, 1932.

16. Pfister, J.: Hundert und dreissig Fälle von Keratitis interstitialis diffusa inclusive fünf Fälle von Keratitis interstitialis centralis annularis nach Vossius, Klin. Monatsbl. Augenh. **28**:114, 1890.

17. Cunningham, J. F.: Analysis of a Series of Cases of Interstitial Keratitis, Tr. Ophth. Soc. U. Kingdom **42**:44, 1922.

18. Derby, G. S.: Interstitial Keratitis, with Special Reference to the End Result, Ophth. Rec. **26**:563, 1917.

19. Anke, R.: Hundert Fälle von Keratitis parenchymatosa diffusa, Centralbl. prakt. Augenh. **9**:360, 1885.

20. Spicer, W. T. H.: Parenchymatous Keratitis, Interstitial Keratitis, Uveitis Anterior, Brit. J. Ophth., Monog. Supp. 1, 1924.

21. Hoehne, H.: Über Keratitis parenchymatosa, Klin. Monatsbl. Augenh. **105**:656, 1940.

22. Klauder, J. V., and Vandoren, E.: Interstitial Keratitis: Analysis of 532 Cases with Particular Reference to Standardization of Treatment, Ven. Dis. Inform. **22**:307, 1941; Arch. Ophth. **26**:408, 1941.

23. Dalsgaard-Nielsen, E.: On Acuity of Vision and Causes of Impairment of Vision in Patients with Past Syphilitic Interstitial Keratitis, Acta ophth. **17**:43, 1939.

24. Nordmann, E.: Das Schicksal der Keratitis parenchymatosa e lue hereditaria, Inaugural Dissertation, Leipzig, 1932.

25. Oksala, A.: Studies on Interstitial Keratitis Associated with Congenital Syphilis Occurring in Finland, Helsinki, Kauppakirjapaino O. Y., 1951; Acta ophth., Supp. 37.

Incidence Unassociated with Interstitial Keratitis.—Green [26] studied the eyegrounds of 100 patients with congenital syphilis ranging in age from less than 1 year to over 12 years. Fifty-two of these 100 patients presented pathologic changes in the eyegrounds. Included in these changes were alterations of the optic nerve and of the vessels. The percentage showing lesions of chorioretinitis could not be determined from his report. It was stated, "There was hardly a single pathologic eyeground that did not present lesions of diverse types; in other words, mixed forms predominated." The impression was gained that the alterations Green observed could not fit into the four types of Sidler-Huguenin. Green classified his findings under six categories: 1. Peripheral, sometimes central, punctate pigmentation, coinciding very closely with Type 1 of Sidler-Huguenin, was presented by 28 patients. 2. Peripheral punctate pigmentation was observed in three patients. 3. Small round white areas with pigmented center and border were observed in several patients. 4. Large, irregular areas of dark, pigment-bordered chorioretinal atrophy were observed in five patients. 5. Masses of gray pigment alternating with depigmented areas were observed in four patients. 6. Disseminated chorioretinitis was observed in two patients.

Of 443 patients with congenital syphilis, White and Veeder [27] observed chorioretinitis in 3.3%.

In the study of Lennarson and Jeans,[28] the eyegrounds of 143 patients with congenital syphilis were examined. One of the 19 infants and 16 (13%) of the older children had chorioretinitis. Their report stated that what is described as the salt-and-pepper fundus was observed in only three patients. No description of the chorioretinitis in the remaining patients is given in the report.

Of Lemoine's [29] 262 patients with congenital syphilis, 20.9% had chorioretinal changes. The salt-and-pepper fundus was observed in 13.35%; chorioretinitis, in 7.25%, and retinitis pigmentosa, in 0.38%. The salt-and-pepper fundus was observed most frequently in the periphery, with predilection for the lower nasal quadrant, or only one segment, or small areas in the periphery, or occasionally throughout the fundus.

The condition diagnosed as chorioretinitis did not present a uniform picture. The process either was disseminated (two patients), with large spots of dark pigment interspersed with extensive areas of choroidal atrophy, or oval or round atrophic spots scattered in the fundus, surrounded by a slight pigment ring, or occurred as lesions with a dark-brown pigment center with a slight halo of atrophy or atrophic lesions without any pigment deposit. These lesions were observed most frequently in the periphery, more frequently down or down and in. Only one patient presented degenerative changes of both maculae, associated with pigment deposits in the fundi.

26. Green, J., Jr.: The Eye in Hereditary Syphilis, Am. J. Dis. Child. **20**:29, 1920.

27. White, P. J., and Veeder, B.: Hereditary Syphilis: A Study of 443 Cases, with Especial Reference to Results of Treatment, Am. J. Syph. **6**:353, 1922.

28. Lennarson, V. E., and Jeans, P. C.: Congenital Syphilis of Eye: Clinical Study, Am. J. Syph. **21**:90, 1937.

29. Lemoine, A. N.: Ocular Manifestations of Congenital Syphilis and Treatment by Induced Hyperpyrexia, Tr. Am. Ophth. Soc. **32**:522, 1934.

In Cernea's[30] study of ocular involvement in congenital syphilis the statement is made that chorioretinitis was present in 70 of 1,500 patients examined. No description of the process was given, nor was the incidence of interstitial keratitis indicated.

In Igersheimer's[13] comprehensive study of ocular syphilis chorioretinitis of congenital syphilis is thoroughly discussed. He observed Type 2 more frequently than Type 1 and attributed this to the association of Type 2 with interstitial keratitis. The opinion was expressed that the yellow or yellowish-red lesions of Type 2 do not necessarily indicate a fresh process, since such lesions may remain unpigmented. He had never observed chorioretinitis appearing after interstitial keratitis in patients whose fundi were normal before onset of interstitial keratitis. He regarded this observation as evidence that the disease originates in early life.

Igersheimer was in accord with the opinion expressed by Hirschberg[9] that chorioretinitis after a pause of about one year may progress from the periphery to the entire fundus. Unlike Sidler-Huguenin, he expressed the belief that this occurrence should be included in the category of Type 2. He was not in accord with Hirschberg, who attributed to congenital syphilis the appearance of chorioretinitis in the second decade of life.

He stated that severe forms of Type 2, which affects the entire fundus, are difficult to differentiate from Type 4, the chorioretinitis pigmentosa which resembles retinitis pigmentosa. Igersheimer asked the question, "Is there a genuine form of retinitis pigmentosa caused by syphilis?" In discussing this, he called attention to Leber's original description of retinitis pigmentosa. In most of Leber's cases the etiology was unknown, but syphilis was suspected in 7.6%.

Types 1, 2, and 4 were the most frequent forms that Igersheimer observed. He rarely encountered Type 3. He was uncertain that what Sidler-Huguenin designated as Type 3 merits a separate category, since in the late stage of Type 3 pigmentation appears and thereby assumes considerable resemblance to Type 2.

In addition to the aforementioned forms, Igersheimer included the central choroidoretinitis of congenital syphilis, as well as choroiditis circumpapillaris, possibly caused by drusen of Bruch's membrane, the ophthalmoscopic picture of which is very similar to drusen.

Sidler-Huguenin's report included a review of all reported cases of retinochoroidal changes of congenital syphilis. Subsequently, such a review was made by Groenouw,[31] Green,[26] and Igersheimer.[13] In our report mention will be made only of pertinent studies subsequent to Igersheimer's report.

In addition to the aforementioned reports of chorioretinitis appearing since Igersheimer's review, mention should be made of reports by Russian investigators and of reports of central choroiditis of congenital syphilis—Agnantis,[32] Kraupa,[33] Harry,[34] and Bonnet.[35]

30. Cernea, R.: Augenerkrankungen bei der konnatalen Syphilis, Munich, Akademischer Verlag, 1947.

31. Groenouw, A., in von Graefe, F. W. E., and Saemisch, E. T.: Handbuch der gesamten Augenheilkunde, Ed. 2, Leipzig, 1904, Pt. 1, Vol. 2, p. 788.

32. Agnantis, C.: Case of Syphilitic Macular Choroiditis, Ann. ocul. **164**:281, 1927.

33. Kraupa, E.: Die kongenital luetische zentrale Retinochoroiditis, Ztschr. Augenh. **89**:204, 1936.

34. Harry, B. H.: Central Retinochoroiditis in Congenital Syphilis, Canad. M. A. J. **38**:381, 1938.

35. Bonnet, P.: Chorioretinitis of Congenital Syphilis, Ann. ocul. **180**:245, 1947.

The impression is gained from the literature that central choroiditis of congenital syphilis is not common, that it is more likely to be unilateral, and that it rarely occurs as an isolated lesion but appears in conjunction with chorioretinal changes elsewhere.[36] In one of the two cases reported by Kraupa [33] the central choroiditis was unilateral; both eyes showed the salt-and-pepper fundus. In the other case the central choroiditis was bilateral; in one eye it was the only lesion. The rarity of the bilateral type is evident by Kraupa's statement that he has seen only two cases in 22 years.

Zacharievska and Goldfeder [37] studied the eyegrounds of 81 patients with congenital syphilis. The ages of these patients ranged from 2 months to 32 years. Of this number, 23 patients were listed as adults. The opinion was stated that chorioretinal changes of congenital syphilis are varied and complex and that considerable experience is required in diagnosis. Of the total number, 75.3% showed alterations in the eyegrounds. This figure, the authors state, is higher than the 43% observed by Archangelsky and Feldman, or the 26.2% observed by Cassel in a similar study The most frequent type observed in their study was Type 1. Comment was made on the variation in size of the lesions in Type 1 and the intensity of the process. Type 2 was the next most frequent; the least frequent was Type 4, which was seen only seven times, and only in patients with late congenital syphilis. Type 3 was not seen.

Type 2 was not observed in infants; however, Type 1 combined with Type 2 was noted in one patient, aged 18 months. In older patients a combination of two types was observed, Type 1 with Type 2 or Type 4, or Type 2 with Type 4. Their series included seven infants from 20 to 10 months of age; three of this number had chorioretinitis of Type 1 in conjunction with optic neuritis. In the entire series optic neuritis and optic atrophy were the most frequent concomitant abnormalities.

In breaking down their series into different age groups, it was observed that 61.1% of infants and patients in early childhood had chorioretinitis, as compared with 74.5% of patients classified as older children. It was noted that in infancy chorioretinitis was the most frequent of all syphilitic manifestations. In its early stage the disease was resistant to treatment. Of the treated patients, 50% had eyeground lesions, as compared with 86% of the untreated patients. It was stated that treatment of the mother during pregnancy combined with early treatment of the infant evidently prevents chorioretinitis.

Tshirkovsky and Rautenstein [38] examined the eyegrounds of 231 children with congenital syphilis in Leningrad from 1929 to 1935. Of this number, 79.6% were

36. Retinochoroiditis juxtapapillaris (Jensen), we feel, need not be considered in a discussion of retinochoroidal changes of congenital syphilis. Apparently it is the consensus that this disease is of variable cause. Acquired syphilis (more likely in the early stage) has been demonstrated or suspected; congenital syphilis is considerably less likely (Verhoeff, F. H.: Tr. Am. Ophth. Soc. **14**:568, 1916. Schertlin, G.: Monatsbl. Augenh. **57**:60, 1916. Igersheimer,[13] p. 240. Fischer, E.: Klin. Monatsbl. Augenh. **72**:500, 1924. Bencini, A.: Boll. ocul. **13**:1129, 1934. Focosi, M.: ibid. **26**:1, 1947).

37. Zacharievska, N. N., and Goldfeder, A. E.: Value of Examination of Ocular Fundus in Diagnosis of Congenital Syphilis, Vrach. delo **18**:443, 1935.

38. Tshirkovsky, V. V., and Rautenstein, E.: Relative Diagnostic Importance of Ocular Changes in Early Congenital Syphilis, Vestnik oftal. **7**:289, 1935.

below 1 year of age; 6.9% were about 2 years of age; the remaining number were less than 5 years of age.

Of the 231 children, 39.4% had florid syphilis (lesions of the skin, mucous membranes, viscera, or osseous system); 60.6% had latent syphilis (without clinical evidence of syphilis).

Forty children (17.3%) had chorioretinitis of Type 1. Of this number, it was poorly manifested in 22, and in 18 it was well marked. Of the 22 children, 11 had florid syphilis, and 11 had latent syphilis. Of the 18 children, 9 had florid syphilis, and 9 had latent syphilis.

The authors stressed the variations in chorioretinitis of Type 1 with reference to the size of the lesions and to its intensity, as well as the variations in the normal eyeground of the infant. Mention was made of the uneven pigmentation of the normal eyeground, the frequency of albinism, and the pronounced speckling of the fundus, or "fundus flavus," of blond children.

Type 2 was observed in two children; one was 20 months old, and the other 5 years of age. Types 3 and 4 were not observed.

One infant, first examined at the age of 2 months, presented "poorly manifested" Type 1. In subsequent examinations in the ensuing four years the disease became "fully developed." This occurred despite continuous antisyphilitic treatment. The authors regarded "poorly manifested" forms of Type 1 without pigmentation as the initial form of the pathologic process, from which gradually develops the "salt-and-pepper" type of chorioretinitis.

The authors stressed the diagnostic importance of the pathologic process in its "poorly developed," as well as in its "fully developed" stage, especially in children with latent syphilis. Conspicuous in their series was its occurrence in the offspring of mothers whose syphilis was untreated.

Archangelsky and Feldman [39] studied the eyegrounds of 270 patients with congenital syphilis. They reported pathologic changes in 131 patients. The following incidence of chorioretinal alterations was observed!

Thirty-nine patients showed changes regarded as Type 1. Of this number, 22 were 3 weeks to 1 year of age, the remainder were from 1 to 15 years of age. Twenty patients (6 months to 25 years of age) presented changes diagnosed as Type 2. This type was seldom seen in infants less than 6 months of age; it was more frequently seen after the age of 5 years. Only one patient showed Type 3, and this was in the pigmented stage. Type 4 was not observed in any of the patients. In 15 patients a combination of types was diagnosed. Classification of these types was not given in the report.

Eleven patients (a few days to 2 years of age) showed what the authors called a yellow-orange tint of the eyeground. This appearance resembled that of the eyeground in leukemia. The retina was cloudy; the optic disk was pale with blurred margins. The vessels showed no change. The authors regarded this change as representing the early stage of Type 1. They expressed the opinion that this form, and also mild forms of Type 1, may disappear or may progress to a severe form of Type 1 or to Type 2. In this sense they did not believe, contrary to Sidler-Huguenin, that Type 1 was always stable.

39. Archangelsky, V. N., and Feldman, V. I.: Characteristic Pathologic Changes of Eyes in Congenital Syphilis, Venerol. i. dermat. **6**:5, 1929.

Chorioretinitis as Described by Some Modern Writers.—In Woods's [40] study of syphilis of the eye, chorioretinitis of congenital syphilis is briefly discussed as of three forms. The first form consists of circumscribed focal lesions, which leave behind heavy white scars with clumps of choroidal pigment. The second form is the well-recognized involvement of the peripheral choroid, which leaves behind the characteristic pigmentation of the peripheral fundus, the so-called "salt-and-pepper" fundus. At times the lesions may be larger and coarser, with spots of choroidal atrophy and gliosis interspersed with heavy deposits of pigment. The third form is the one that closely simulates primary degeneration of the retina.

Walsh [41] discussed the pathologic process as (1) the "salt-and-pepper" fundus; (2) circumscribed chorioretinitis; (3) retinal scarring with atresia of blood vessels and optic atrophy, and (4) retinitis pigmentosa. He expressed the opinion that "retinitis pigmentosa" may occur in (1) the classic disease in nonsyphilitic patients, (2) in syphilitic patients, (3) as part of cerebromacular degeneration, and (4) as part of some unexplained infection.

Duke-Elder [42] wrote that chorioretinitis of congenital syphilis assumes many forms and presents a heterogeneous array of clinical pictures. He divided the disease into the following groups: (*a*) the finely pigmented, or pepper-and-salt, fundus; (*b*) isolated pigment spots, usually two or three in number and scattered in the peripheral fundus; (*c*) grossly pigmented areas forming large black masses in the fundus, in circumscribed areas or throughout the periphery, and (*d*) white atrophic areas scattered over the fundus, either in disseminated form or occurring as large confluent patches in the central area.

He expressed the opinion that these types should not be taken as entities, for mixed pictures appear, different areas of the fundus showing different characteristics. Sometimes the changes are widespread, or they are confined to the posterior region or to the periphery, especially when associated with interstitial keratitis; occasionally the macula is involved in a central choroiditis.

In Berens' [43] and in Troncoso's [44] texts, chorioretinitis of congenital syphilis is not discussed. In Elwyn's [45] volume, discussion of this process is essentially a description of the four types described by Sidler-Huguenin.

Tassman [46] stated:

> Choroiditis or chorioretinitis, as a manifestation of hereditary syphilis, may occur in many different forms and either alone or in association with such other manifestations as interstitial keratitis. The most common form which is characteristic is the condition known as the "salt and pepper fundus."

40. Woods, A. C.: Syphilis of the Eye, Am. J. Syph. **27**:133, 1943.

41. Walsh, F. B.: Clinical Neuro-Ophthalmology, Baltimore, Williams & Wilkins Company, 1947, pp. 659-660.

42. Duke-Elder, W. S.: Text-Book of Ophthalmology, Vol. 2, St. Louis, C. V. Mosby Company, 1940, pp. 2273-2274.

43. Berens, C., Editor: The Eye and Its Diseases, Ed. 2, Philadelphia, W. B. Saunders Company, 1949.

44. Uribe y Troncoso, M.: Internal Diseases of the Eye and Atlas of Ophthalmoscopy, Ed. 2, Philadelphia, F. A. Davis Company, 1950.

45. Elwyn, H.: Diseases of the Retina, Philadelphia, The Blakiston Company, 1946.

46. Tassman, I. S.: Eye Manifestations of Internal Diseases (Medical Ophthalmology), St. Louis, C. V. Mosby Company, Ed. 3, 1951, p. 359.

A description of this form follows.

Pigment spots in the choroid, as manifestations of hereditary syphilis, may be found either singly or in larger numbers without other objective evidences. There may be only one or two isolated spots of pigment in the periphery of the fundus which are nearly as large as the disc. In other instances the lesions may be characterized by a number of atrophic white areas in the periphery of the fundus, or there may be only one or two areas, sometimes seen in the neighborhood of the macula, which are white in color and reveal some pigment within or around the edges.

In Schieck and Brückner's "Handbuch" [47] the four types of Sidler-Huguenin are briefly discussed (with illustrations).

Fuchs [48] described the four types of Sidler-Huguenin and concluded as follows, "It is often difficult to differentiate the four types from each other because of transitional cases."

REPORT OF STUDY

In our study we examined 223 patients who had interstitial keratitis and 71 patients with congenital syphilis who had not had interstitial keratitis. Examination of these patients was conducted after use of a mydriatic.

Of the patients with interstitial keratitis, 66.6% were females and 33.4% were males; 63% were white persons and 37% were Negroes. The majority were between 8 and 25 years old; relatively few were below 8 or over 30 years of age. In some patients corneal opacity did not permit satisfactory examination of both fundi. It was therefore not possible to determine the incidence of unilateral and bilateral changes in the fundus. Patients were included in whom a fair view of one or both fundi was obtained. It is possible that in some of these patients chorioretinal changes may have been missed.

The 71 patients with noninterstitial keratitis were divided into two groups. Group 1 comprised 54 children without ocular complaint whom we examined in syphilitic clinics of various hospitals. Group 2 comprised 17 patients, mostly adults, who had visual complaint and were patients in the clinics at Wills Eye Hospital. They were referred to our clinic on account of syphilitic infection, which we regarded as congenital. Of these patients, six had optic atrophy (Case 3; Fig. 7 *B*) as part of neurosyphilis; three had retinitis pigmentosa (Fig. 8), and some of the others had chorioretinal changes (Fig. 7*A*). The incidence of such changes is therefore higher in this group than in patients in Group 1. For statistical reasons the two groups are separated.

Of the 223 patients with interstitial keratitis, 30, 13.4%, had chorioretinal changes and 18 had perivasculitis, 8% (Case 1; Figs. 5 and 6). In some patients perivasculitis was observed as the only fundal lesion.

Of the 54 patients with noninterstitial keratitis, comprising Group 1, 4 had chorioretinitis and 3 had perivasculitis. Of the 17 patients comprising Group 2, 8 had chorioretinitis (Case 2; Fig. 7, left), and 5 had perivasculitis (Fig. 7 *A* and *B*).

In the total of 42 patients with chorioretinitis, it was difficult to classify the disease under the four types of Sidler-Huguenin.

47. Schieck, F.: Die syphilitischen Netzhauterkrankunger, in Schieck, F., and Brückner, A.: Kurzes Handbuch der Ophthalmologie, Berlin, Julius Springer, 1930, Vol. 5, pp. 535-538.

48. Fuchs, A.: Diseases of the Fundus Oculi with Atlas, Ed. 1, Philadelphia, The Blakiston Company, 1949, p. 184.

The alterations we observed were for the most part a disturbance of pigment distribution. The fundus picture of five patients suggested the salt-and-pepper type (Case 1; Fig. 5, right), although it was not a classic representation. In others

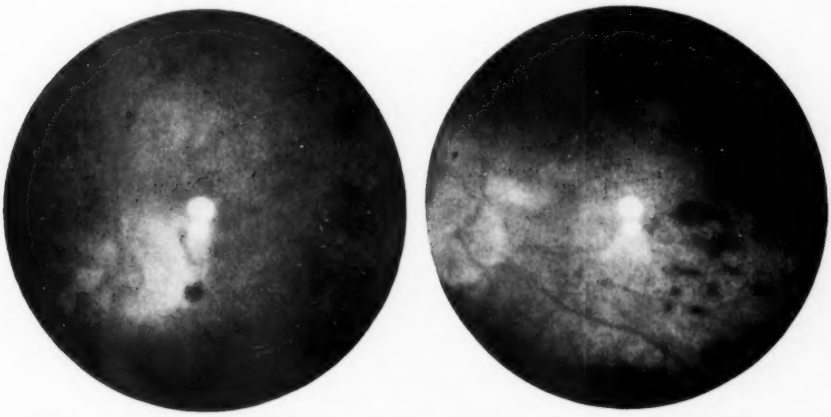

Fig. 5.—Left, acute unilateral interstitial keratitis. The uninvolved eye (photograph) showed disseminated retinochoroiditis with plaques of pigment about the macula, perivascular sheathing, and white exudates. Visual acuity was 6/60, correctible to 6/21.

Right, fundus of the left eye of patient discussed in Case 1, showing diffusely scattered pigment deposits. They were clump-like, and there were no patches of retinochoroidal atrophy.

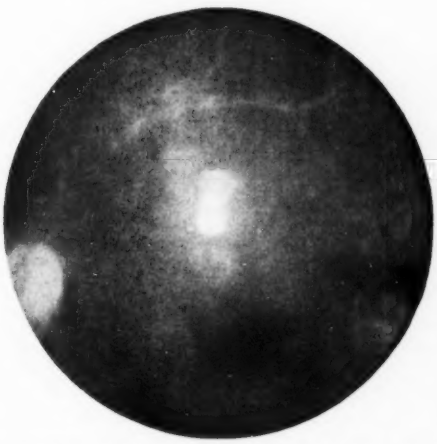

Fig. 6.—The patient, aged 21, had congenital syphilis and old interstitial keratitis. The left eye (shown in photograph) presented pigmented patches of choroiditis in the nasal periphery, above and to the temporal side of the macula and extending to the periphery. In the right eye there were sparse, small, rounded pigment deposits confined to the periphery. Perivasculitis was pronounced in both eyes. Corrected visual acuity was 6/15 in the right eye and 2/60 in the left eye.

the pigment lesions were larger than the size of pepper or of snuff granules. They were coarser, of variable size, and arranged either as discrete, rounded, ringed areas or as a solid patch of black (Figs. 5 and 7, left; Cases 1 and 2).

The minimal changes of pigment distribution comprised a sparse number of discrete lesions in the periphery (right eye, Fig. 6). Oftener the pigmentary changes were not confined to the periphery but occurred also in the midzone, with a variable number of pigmentary changes. Only in some patients were the changes widespread

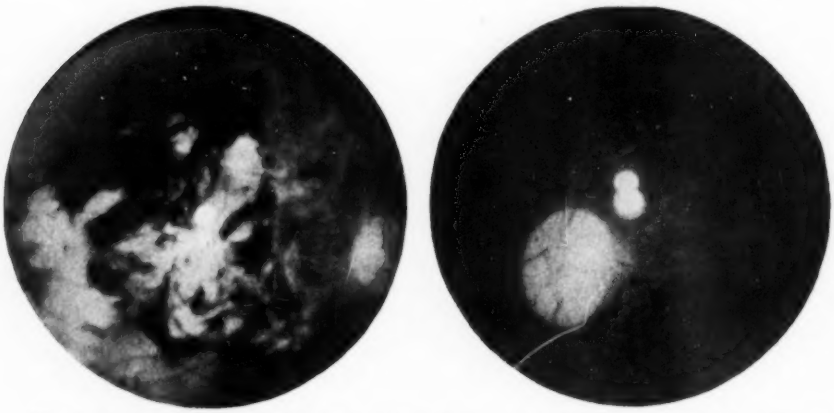

Fig. 7.—Left, fundus of right eye of patient discussed in Case 2, showing retinochoroidal atrophy with heavy pigment deposits. These lesions were diffusely scattered over the fundi of both eyes. Perivasculitis was generalized and pronounced.

Right, fundus of left eye of patient discussed in Case 3, showing perivasculitis which was generalized and pronounced in both fundi.

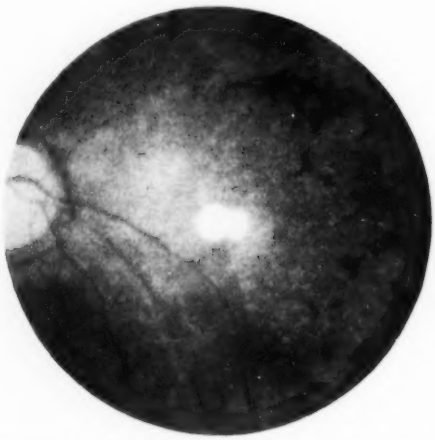

Fig. 8.—Retinitis pigmentosa in a patient aged 20. The history and other evidence (including deafness) suggested congenital syphilis. The Wassermann reaction was positive. Both optic disks were of good color; there was heaping up of pigment in the midzone, not lacy, but ropy and in areas clump-like, without perivascular distribution. The vessels showed some constriction; the macular region and periphery were not involved. Visual acuity was 6/12 with correction in each eye. The peripheral fields showed marked concentric contraction.

(Case 2; Fig. 7, left). In a limited number of patients there were patches of atrophy with the pigment deposits (Case 2; Fig. 7, left). These patches were variable in size, but usually small, and were sparse.

When the aforementioned alterations were observed, it was exceptional that the periphery was uninvolved (Fig. 8).

No frank cases of Type 3 were noted. We were undecided whether the following changes could be included in this category. Three patients presented only ring-like zones of depigmented uvea with scalloped edges. These were predominantly in the periphery, but were noted elsewhere and became more scattered toward the posterior pole.

In terms of Sidler-Huguenin's classification, our cases, excluding the cited exceptions, could be regarded as instances of severe forms of either Type 1 or Type 2.

Retinitis Pigmentosa.—This type was not observed in the 223 patients with interstitial keratitis or in the 54 patients with noninterstitial keratitis in Group 1. As aforementioned, retinitis pigmentosa was observed only in three patients in Group 2 and is illustrated in Figure 8.

In our experience, therefore, retinitis pigmentosa of congenital syphilis is rare; moreover, we have never observed the disease that could be attributed (as some writers have) to acquired syphilis. Its infrequency is apparent in the more recent reports.[49] We believe that syphilis is now overemphasized as an etiologic factor.

The following considerations serve to differentiate retinitis pigmentosa of congenital syphilis from the primary form and from what has been called (Duke-Elder [50]) the secondary types of retinitis pigmentosa: the history of syphilis in the parents, and the presence of old interstitial keratitis or other evidence of congenital syphilis. The serologic tests for syphilis are not decisive. A positive reaction may be coincidental; a negative reaction may have occurred spontaneously or have followed treatment. Evidence of former uveitis would be more likely in the syphilitic type, in contrast to the primary type.

The older clinicians stressed the diagnostic value of fine, dust-like opacities in the anterior part of the vitreous in syphilitic involvement of the uveal tract. Apparently, this criterion did not differentiate congenital and acquired syphilis. Our observations tend to minimize the importance of this finding in diagnosis of syphilitic uveitis; nevertheless, its presence is not to be expected in primary retinitis pigmentosa.

The beeswax color of the optic disk and posterior polar cataract, characteristic of the primary type, we believe, does not occur in the syphilitic type. As aforementioned, Sidler-Huguenin regarded a bluish-gray color of the peripapillary zone as characteristic of the syphilitic type. In the latter, the blood vessels are less contracted; pigmentary changes are coarser, with greater tendency to clumping, are less likely to follow vascular distribution, are more scattered, and do not tend, as in the primary type, to be of equatorial distribution.

Perivascular sheathing, as discussed in the foregoing discussion, is much more likely to occur in the syphilitic type. Of 40 consecutive patients with primary retinitis pigmentosa whom we examined for this study, perivascular sheathing was present in 1. She was a Negro aged 38; there was no history or clinical or serologic

49. Dalsgaard-Nielsen.[23] Nordmann.[24] Oksala.[25] Zacharievska and Goldfeder.[37] Tshirkovsky and Rautenstein.[38] Archangelsky and Feldman.[39]

50. Duke-Elder, W. S.: Text-Book of Ophthalmology, St. Louis, C. V. Mosby Company, Vol. 2, p. 2766.

evidence of syphilis. Nevertheless, perivasculitis suggested the congenital syphilitic type of retinitis pigmentosa. In support of this is the rarity of the primary type of the disease in the Negro, this patient being the only Negro in our series of 40 patients.

The age of onset and the course of the disease are different in the two diseases. In the primary type night blindness occurs in the first decade of life. Progress is slow, often with remissions. In the second decade visual loss is troublesome, and by the 30's is incapacitating in many cases. The syphilitic type follows a more benign course.

In the primary type a ring scotoma occurs early—the loss at first being only for color, with progressive, slow loss to tubular vision and incapacity. In the syphilitic type, ring scotomas also occur in the early stage, but the clinical course usually is more benign. Some writers state as a differential point that the scotoma is at the equator in the syphilitic type and at about the 20- to the 30-degree meridian in the primary type.

In spite of these criteria, differential diagnosis may be difficult; indeed, it cannot be made with certainty. This applies especially to cases in which classic signs of the primary type of disease are absent.

Central Choroiditis.—Of the 42 patients with chorioretinitis, involvement of the macula occurred bilaterally in 3. Two of these patients are discussed in Cases 2 and 3, and the fundi of the eyes are shown in Figure 7*A* and *B*. Two of the three patients were industrially blind in both eyes.

Involvement was unilateral in six patients. Case 1 and Figures 5, right, and 6 concern two of these five patients. Four of these five patients were industrially blind only in the eye in which the macula was affected. Macular involvement of all these patients was associated with chorioretinal changes elsewhere.

CHORIORETINITIS AS A CAUSE OF INDUSTRIAL BLINDNESS

In addition to these two patients, two other patients were industrially blind in both eyes. One had retinitis pigmentosa (Fig. 8); another had disseminated chorioretinitis.

This percentage of industrial blindness in both eyes is high in relation to the total number of patients with chorioretinitis, but not in relation to the total of 294 patients with congenital syphilis. Chorioretinitis is therefore not as important a cause of industrial blindness as is interstitial keratitis and atrophy of the optic nerve of acquired syphilis.

Perivasculitis.—This condition was a distinctive observation in our study (Cases 1, 2, and 3; Figs. 5, 6, 7). It was manifested as a pale streak bordering the vessels. Either or both arteries and veins were affected. Involvement was usually localized rather than general and affected the peripapillary or the posterior polar region oftener than the periphery. In patients with less pronounced vascular changes, search was required to detect the small area involved, whereas in patients with pronounced changes the perivascular streaking was diffuse and marked by encroachment on the caliber of the vessels. In cases of still more pronounced changes the vessels were obliterated and represented by a white scarred streak. Hemorrhages and retinal exudates (excluding the perivasculitis itself) were not observed.

Perivasculitis was observed with and without other fundal lesions in both the patients with interstitial keratitis and the patients with noninterstitial keratitis.

Three of six patients (Group 2) with atrophy of the optic nerve had perivasculitis. In one (Case 3; Fig. 7, right) it was associated with chorioretinitis. All the three patients had clinical evidence of neurosyphilis, and two had characteristic abnormalities of the spinal fluid. The question arose whether atrophy of the optic nerve was secondary to perivasculitis or was part of the neurosyphilis. We are inclined to the latter explanation.

As discussed in Case 3, perivasculitis was of aid in diagnosing congenital syphilis. Other instances could be cited in which the presence of perivasculitis in a child or a young adult was helpful or was decisive in diagnosing syphilis as congenital. In the older literature (Holmes [51]) perivasculitis is stressed as one of the eyeground changes in congenital syphilis, and this phase was comprehensively discussed (and illustrated) by Igersheimer.[13] We do not believe that modern texts sufficiently discuss this pathologic alteration or stress its diagnostic importance.[52] Its presence in a young child or an adult in the absence of other explanation constitutes, we believe, considerable evidence of congenital syphilis. To demonstrate its presence is one among other reasons for ophthalmologic examination of patients with syphilis as an aid in determining the status of their infection.

In Friedenwald's [12] histologic study of the eyes of syphilitic infants, he observed that spirochetes were most constantly found in the sheaths of blood vessels as they enter the eye. This may serve in part to explain the occurrence of perivasculitis of the fundal vessels in congenital syphilis. Its occurrence in acquired syphilis, in our experience, is rare.[53]

Diagnosis of Chorioretinitis of Congenital Syphilis.—We regard the following features as diagnostic: (1) the salt-and-pepper fundus; (2) the peripheral localization of the disease or its predominance in that region; (3) its association with perivasculitis. Other concomitant symptoms of diagnostic aid are evidence of old interstitial keratitis, clinical evidence of congenital syphilis, or the suggestion of such infection from the history. As previously mentioned, the serologic tests for syphilis are not decisive.

Status of Sidler-Huguenin's Classification.—It becomes apparent how varied and complicated are the alterations of the eyegrounds in congenital syphilis and how different the description by different authors. Sidler-Huguenin expressed the opinion that the ophthalmoscopic picture at first glance appears complicated but that on careful search the various forms can be found. Subsequent investigators, including ourselves, are not entirely in accord with this opinion.

We agree with the statement of Zacharievska and Goldfeder [37] and others that Sidler-Huguenin's classification is of no great practical value. We believe these types are too arbitrary; they exist essentially in print and as illustrations, and not in

51. Spicer, W. T. H.: Retinal Vasculitis in Inherited Syphilis, Tr. Ophth. Soc. U. Kingdom **12**:116, 1892.

52. An exception is the following statement by Elwyn [45]: "Occasionally the fundus picture in congenital syphilis presents itself mainly in the form of vascular changes. The disc is pale, the retinal vessels are narrowed and are accompanied by white lines or they are completely covered by white sheaths."

53. Such rarity is not implied in Elwyn's [45] discussion of syphilis of the retinal vessels.

evidence of syphilis. Nevertheless, perivasculitis suggested the congenital syphilitic type of retinitis pigmentosa. In support of this is the rarity of the primary type of the disease in the Negro, this patient being the only Negro in our series of 40 patients.

The age of onset and the course of the disease are different in the two diseases. In the primary type night blindness occurs in the first decade of life. Progress is slow, often with remissions. In the second decade visual loss is troublesome, and by the 30's is incapacitating in many cases. The syphilitic type follows a more benign course.

In the primary type a ring scotoma occurs early—the loss at first being only for color, with progressive, slow loss to tubular vision and incapacity. In the syphilitic type, ring scotomas also occur in the early stage, but the clinical course usually is more benign. Some writers state as a differential point that the scotoma is at the equator in the syphilitic type and at about the 20- to the 30-degree meridian in the primary type.

In spite of these criteria, differential diagnosis may be difficult; indeed, it cannot be made with certainty. This applies especially to cases in which classic signs of the primary type of disease are absent.

Central Choroiditis.—Of the 42 patients with chorioretinitis, involvement of the macula occurred bilaterally in 3. Two of these patients are discussed in Cases 2 and 3, and the fundi of the eyes are shown in Figure 7*A* and *B*. Two of the three patients were industrially blind in both eyes.

Involvement was unilateral in six patients. Case 1 and Figures 5, right, and 6 concern two of these five patients. Four of these five patients were industrially blind only in the eye in which the macula was affected. Macular involvement of all these patients was associated with chorioretinal changes elsewhere.

CHORIORETINITIS AS A CAUSE OF INDUSTRIAL BLINDNESS

In addition to these two patients, two other patients were industrially blind in both eyes. One had retinitis pigmentosa (Fig. 8); another had disseminated chorioretinitis.

This percentage of industrial blindness in both eyes is high in relation to the total number of patients with chorioretinitis, but not in relation to the total of 294 patients with congenital syphilis. Chorioretinitis is therefore not as important a cause of industrial blindness as is interstitial keratitis and atrophy of the optic nerve of acquired syphilis.

Perivasculitis.—This condition was a distinctive observation in our study (Cases 1, 2, and 3; Figs. 5, 6, 7). It was manifested as a pale streak bordering the vessels. Either or both arteries and veins were affected. Involvement was usually localized rather than general and affected the peripapillary or the posterior polar region oftener than the periphery. In patients with less pronounced vascular changes, search was required to detect the small area involved, whereas in patients with pronounced changes the perivascular streaking was diffuse and marked by encroachment on the caliber of the vessels. In cases of still more pronounced changes the vessels were obliterated and represented by a white scarred streak. Hemorrhages and retinal exudates (excluding the perivasculitis itself) were not observed.

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53. Such rarity is not implied in Elwyn's [45] discussion of syphilis of the retinal vessels.

clinical reality. We regarded his classification as a "starting point" in study, and possibly, too, one to be used for teaching purposes.

From a pragmatic and teaching standpoint, we believe the essential consideration is the salt-and-pepper fundus and Type 4—retinitis pigmentosa. Other chorioretinal changes of congenital syphilis embrace variable sizes and configurations of pigment and atrophic lesions, which vary in number and location. As aforementioned, the diagnostic features concern peripheral location and association with perivasculitis.

The incidence of chorioretinal changes in congenital syphilis has apparently decreased since the study of Sidler-Huguenin. It is conceivable that the severity of such changes has likewise diminished. The incidence and severity of other symptoms of congenital syphilis have diminished. Dacryocystitis, formerly a common manifestation of congenital syphilis, is now rarely seen. This applies also to the Hutchinson triad and to rhagades. The rarity of these symptoms is not entirely attributable to the decrease in incidence of congenital syphilis, since for some years we have rarely observed these symptoms in patients with interstitial keratitis. For example, the patient represented in Figure 9 is rare among outpatient clientele.

Fig. 9.—The patient on admission had dacryocystitis attributed to congenital syphilis. She had stigmas of the infection, of which the physiognomy and saddle nose are shown in the photograph, and bilateral disseminated retinochoroiditis. Visual acuity was 6/60 in each eye, with and without correction. Soon after admission she had initial onset of interstitial keratitis. Comment is made in the text of the infrequency now of such multiple symptoms of congenital syphilis, and the relative infrequency of retinochoroiditis as a cause of industrial blindness.

She was first seen because of dacryocystitis of congenital syphilis. Examination disclosed many stigmas of congenital syphilis, and disseminated chorioretinitis. Subsequently, bilateral interstitial keratitis developed.

Case (Fig. 5, right).—*An impure form of salt-and-pepper fundus.*

D. E., a white girl, was 11 years of age when first seen, in 1930, with bilateral interstitial keratitis.

She was observed at intervals during the ensuing 21 years. The Wassermann reaction became negative. She married and had a healthy child.

As of October, 1951, visual acuity was 6/60, correctible to 6/9 in the right eye and 1/60, correctible to 6/60, in the left eye. The media of the right eye were clear; the disk was somewhat pale and was covered with glial tissue and perivascular sheathing in the prepapillary region. There was diffuse pigmentary disturbance, marked by dark stippling interspersed with lighter areas, suggestive of a salt-and-pepper fundus. These changes were accentuated about the macular region and the periphery. There were no areas of clumped pigment or retinochoroidal patches.

The media of the left eye were clear; the disk was of fair color. There were diffusely scattered pigment deposits throughout the fundus; these did not follow a vascular distribution. They

were clump-like rather than lacy in appearance. There was no tendency toward greater concentration in the equatorial zone. There were no discrete atrophic retinochoroidal patches. There were some prepapillary glial deposits and perivascular sheathing and a suggestion in the background of a salt-and-pepper picture.

CASE 2 (Fig. 7, left).—*Diffuse retinochoroiditis with involvement of the macula in congenital syphilis; generalized perivasculitis.*

L. Q., a white boy, when first seen, in May, 1941, was 14 years of age. About one month previously he first had difficulty in seeing the blackboard in school, for which reason he came to the clinic. When he was 10 years of age, he was hit in the right eye with a snowball.

Although he presented no stigmas of congenital syphilis, the Wassermann reaction was strongly positive, 44400.

Visual acuity was 6/60, correctible to 6/30, in the right eye and 6/30, correctible to 6/21, in the left eye. There were a few dense, coarse vitreous opacities. The optic disks were of good color, flat, with well-defined margins. Perivasculitis was generalized and pronounced. There were diffusely scattered areas of retinochoroidal atrophy with heavy pigment deposits. These varied in size from ¼ disk diameter to larger conglomerate patches, the largest of which was seen in the macular region. They measured about 5 disk diameters, with several satellite patches. The diffusely scattered retinochoroiditic lesions had a tendency toward peripheral distribution.

From May, 1941, to September, 1943, treatment consisted of a total of 61 injections of a bismuth compound and 33 injections of an arsenical. Examination at intervals until 1951 showed no change in the retinochoroiditis, and the visual acuity remained unchanged. The Wassermann reaction in February, 1951, was 30000. The patient remained free of interstitial keratitis.

The positive serologic reaction in the 14-year-old patient suggested congenital syphilis, a diagnosis which was substantiated by the bilateral retinochoroiditis and perivasculitis. Since the central choroiditis was bilateral, it was doubtful whether such alteration could be attributed to the history of injury to the right eye.

CASE 3 (Fig 7, right).—*Primary optic atrophy; neurosyphilis, tabetic type; congenital syphilis suggested by examination of fundi.*

N. W., a Negro woman aged 28, was first seen in December, 1946. As long as she could remember, she had had poor vision. She was an only child, and her parents were dead. She recalled that when "a child" she had been taken to a clinic for "injections." In addition, for several years prior to admission she had received injections at irregular intervals for "bad blood."

There were no stigmas of congenital syphilis. The upper central incisors had been extracted. She had Argyll Robertson pupils; the patellar and Achilles reflexes were absent, and the Romberg sign was positive. The spinal fluid was negative in all phases. The Wassermann reaction of the blood was 44444. Visual acuity was 3/60 in the right eye and 6/60 in the left eye.

The optic disks were paper-white; their margins were well defined. The maculas were heavily pigmented, with atrophic spots indicative of an old, burnt-out central choroiditis. There was sparse sprinkling of the fundi with pigment spots, with punctate dots, and with punctate areas of pallid chorioretinal atrophy. Most striking were vascular changes—perivasculitis. Some vessels were seen only as white streaks. Vascular constriction was general and pronounced.

The perimetric fields showed considerable concentric contraction for white, with somewhat greater loss of the nasal fields. There was, however, no striking evidence of nasal hemianopsia.

The patient was observed at intervals up to April, 1951. On account of irregular attendance, only intermittent treatment with metal chemotherapy was administered. There was no unfavorable progress of the optic atrophy. Visual acuity and perimetric fields remained unchanged.

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INFECTION OF EYE DUE TO PSEUDOMONAS AERUGINOSA TREATED WITH POLYMYXIN B AND "VARIDASE"

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INFECTIONS of the eye due to virulent strains of Pseudomonas aeruginosa have a serious prognosis. Treatment has been relatively ineffective, as evidenced by the large number of patients undergoing enucleation or having severe loss of vision after such infections. The combined use of polymyxin B and "varidase" (streptokinase-streptodornase) were of distinct therapeutic help in the case to be reported.

It has been demonstrated that polymyxins are superior to all other antibiotics in the treatment of infections produced by Ps. aeruginosa. Currently, polymyxin B is available for therapeutic purposes. If the total daily dose of this agent is kept below 2.5 mg. per kilogram of body weight, the chances of the patient's having toxic reactions, such as renal damage or neurological lesions, are minimal. It would appear, also, that the dangers of tissue sensitization from the local use of the polymyxins are slight.

"Varidase" is a tool for the removal of fibrin and pus. Through its catalytic and enzymatic properties, "varidase" effects the hydrolysis of fibrin and desoxyribonucleoprotein. It facilitates the action of humoral forces and drugs and hastens the normal process of repair. This agent has a wide clinical application. Its usefulness is not limited to the field of general surgery.

The lysis of the purulent exudate, particularly of desoxyribonucleic acid, enhances the action of leucocytes.[1] The removal of the pus also permits more effective contact of the chosen antibiotic, in this case polymyxin B, with the bacteria.

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1. Johnson, A. J.: Cytological Studies in Association with Local Injections of Streptokinase-Streptodornase into Patients, J. Clin. Invest. **29**:1376-1386 (Oct.) 1950.

REPORT OF A CASE

A white man aged 44 was admitted to the eye service of the Veterans Administration, Fort Howard, Md., on Dec. 13, 1950, with severe pain in the left eye. On Dec. 8, while he was drilling a piece of metal, a small fragment of the material lodged in his left cornea. On Dec. 11 the eye became extremely painful. With the use of topical anesthesia induced with tetracaine, a foreign body deeply embedded in the cornea was removed and a small rust ring curetted. Aureomycin ointment was instilled, and the patient was sent home to use butacaine (butyn®) and nitromersol (metaphen®) ointment. On the next day he was still uncomfortable and was found to have a deep crater with a rust ring in the lower portion of the cornea. There was slight infiltration at the edges of the wound. The rust ring was curetted; bacitracin ointment was instilled, and he was instructed to apply aureomycin ointment every three hours at home. Two days after the removal of the foreign body, infiltration was still present about the corneal defect. A small area stained with fluorescein. The patient was instructed to apply hot compresses and continue use of the aureomycin at home. On the same evening pain became severe and he was admitted to the hospital.

On the following morning, there were moderate injection of the eye and considerable mucopurulent exudate in the lower cul-de-sac. An area of dense gray infiltration, 2.5 mm. in diameter, with a dirty, ulcerated center, was present. Slit-lamp examination showed an infiltration occupying almost the entire lower nasal quadrant of the cornea. The epithelium was intact except over the ulcer. The infiltration involved the subepithelial tissues and the anterior stroma. Keratic precipitates were not noted. No aqueous ray was noted, and no cells were seen in the anterior chamber. The iris, lens, and fundus appeared normal. The visual acuity was 20/20 in the right eye and was limited to counting fingers at 1 ft. (30 cm.) in the left eye.

The ulcer was cauterized with 3.5% tincture of iodine. Aureomycin and penicillin were administered locally and systemically. A culture yielded a pure growth of Ps. aeruginosa. A typical ring abscess had formed by the following morning. The ulcer and area of infiltration were curetted and cauterized with 3.5% tincture of iodine. At this time the patient was placed on treatment with chloramphenicol and streptomycin, administered systemically and locally. Drops of half-strength vinegar were instilled into the eye. These medications did not help, and on the next day the infiltration had spread to the entire cornea, with a crescent-shaped ulcer extending through the stroma at the nasal side.

All current medications were stopped, and the patients was given 0.1 gm. of polymyxin B [2] every six hours intramuscularly. He also had an eye bath of 0.04 gm. of the drug in 100 cc. of isotonic sodium chloride solution every hour. On Dec. 17 a slight decrease in the amount of exudate and some clearing of the cornea were noted. The appearance of red blood cells, casts, and albumin in the urine and an elevation of the nonprotein nitrogen forced discontinuance of the systemic administration of the polymyxin B.

It was evident that the thick mucopurulent exudate prevented effective antibiotic action. For the next three days the patient received an eye bath of "varidase," containing 20,000 units of streptokinase and 12,000 units of streptodornase,[3] every four hours. The combined treatment was effective. The cornea cleared remarkably, and the exudate almost completely disappeared. All treatment was discontinued on Dec. 26.

On Jan. 5, 1951, acute inflammation was again seen in the eye. The cornea again became densely infiltrated, and a necrotic area developed at the center. Bacteria were not found on smears of scrapings, and the cultures were sterile. Polymyxin B was given topically for three days, with improvement. A small perforation was seen in the lower center of the cornea on Jan. 11. A successful closure was obtained with the use of a sliding conjunctival flap. Improvement was slow but continuous, with the eye becoming white and the temporal cornea clear. When the patient was last seen, on April 20, a dense, vascularized leukoma occupied the center and nasal portions of the eye. The temporal cornea has remained clear. The patient can count fingers at 2 ft. (60 cm.).

2. The polymyxin B was supplied by Burroughs Wellcome & Company, Inc.

3. The "varidase" was supplied by the Lederle Laboratories Division, American Cyanamid Company.

The virulence of this strain of Ps. aeruginosa was tested in two rabbits. The eyes were inoculated by a 25-gauge needle thrust once into the anterior stroma of the cornea. A definite abscess was noted within 12 hours. By 24 hours a ring abscess had formed. All four eyes perforated within six days, two within four days of inoculation.

SUMMARY

The salvage of an eye infected with a virulent strain of Ps. aeruginosa occurs infrequently. Use of polymyxin B and "varidase" (streptokinase-streptodornase) at an earlier period in the course of the patient's illness might have saved more vision. It is suggested that these agents be given further trial in the treatment of severe infections of the eye due to Ps. aeruginosa. The prophylactic use of these drugs is also suggested when infection with this bacteria is suspected, particularly when a foreign body is in the eye, to prevent possible serious effects.

CHRONIC MEMBRANOUS CONJUNCTIVITIS

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THE PURPOSE of this communication is to report the occurrence of two cases of chronic membranous conjunctivitis of unknown origin in white brothers aged 1 and 4 years. These cases are of interest because they have received an extensive etiologic study without a definite bacterial, fungous, or viral agent being established. In both cases extensive treatment with antibiotics and cortisone has been carried out. In addition, in the first case surgical treatment, x-rays, and Streptococcus vaccine were also employed. In neither case has there been any permanent effect upon the membranes. This result has prompted a consideration of the possibility that the disease in these two cases may be a primary tissue aberration related to the general group of ocular pemphigus. A number of similar cases have been reported in the literature from time to time, and an excellent review has been published by Hogan.[1]

SUMMARY OF CASES

CASE 1.—The older brother was first seen when 2 years old. He had a history of thickened, reddened upper lids with conjunctival membranes since the age of 2 weeks. He had previously been treated with local and systemic administrations of penicillin and sulfonamides and by excision of the tarsus of the left upper lid. Examination revealed a well-developed and well-nourished boy in good general health with thickened and reddened upper lids, both lids being covered on their conjunctival surfaces by a thick white membrane (Fig. 1). The other mucous surfaces of the body were normal. The membrane of the right upper lid was flattened to conform to the shape of the globe and arose from a pedunculated base along the upper third of the tarsus. Bleeding occurred when the base was torn away. The membrane of the left upper lid was thinner but was firmly adherent over the entire tarsal area, which bled profusely when the membrane was removed. There was a mucopurulent discharge; the palpebral conjunctiva of the lower lids was red and velvety, but there was only one small patch of membrane near the outer canthus in the left eye. The bulbar conjunctiva was not involved; the cornea did not stain, and there were no scars. The intraocular structures were normal. The lacrimal apparatus functioned normally, and there was no lymphadenopathy. The child was hospitalized twice during the following year for biopsies, bacteriological study, and treatment. At various times, hemolytic and nonhemolytic streptococci and Micrococcus pyogenes var. albus were isolated in cultures on blood agar, but the only organism appearing regularly was a Type XIX Pneumococcus. The cultures on Sabouraud's and Dubos' media for fungi and tubercle bacilli were sterile, and egg-membrane and mouse-brain inoculations for virus gave negative results. Biopsy always showed a subacute inflammatory reaction and edema of the conjunctiva, with a fibrinous membrane arising from a dehiscence of the epithelium and spreading out over the conjunctiva (Fig. 2).

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1. Hogan, M. J.: Conjunctivitis with Membrane Formation, Am. J. Ophth. **30**:1495, 1947.

Fig. 1.—Membrane covering palpebral conjunctiva of right upper lid.

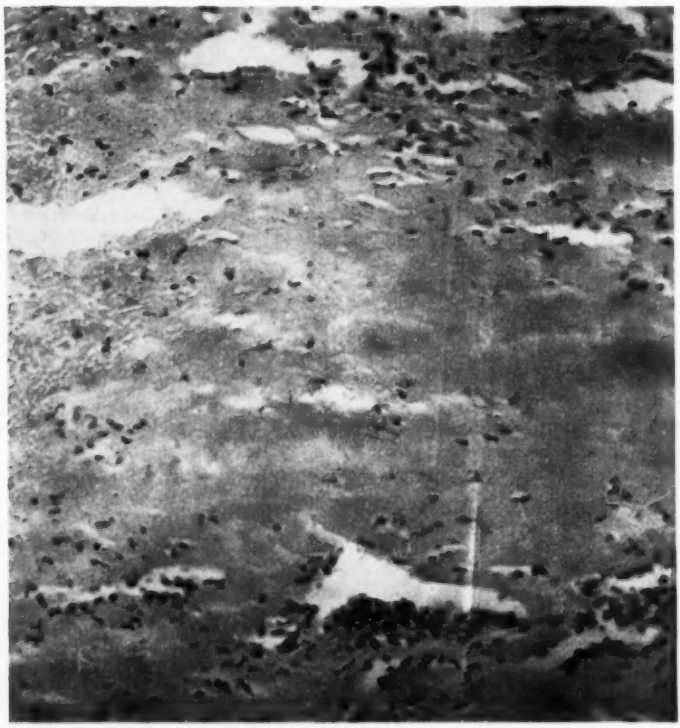

Fig. 2.—Biopsy section showing exudative reaction and chronic inflammation in conjunctival stroma beneath membranes; × 400.

Throughout this year the membranes were removed repeatedly but always recurred within 48 hours, no matter what type of treatment was employed at the time. Local and systemic administrations of penicillin, sulfonamides, and aureomycin were effective in sterilizing the conjunctiva and tissues, as shown by culture of biopsy specimens, but, although the redness of the lids and the discharge could be controlled, the membranes were unchanged. Local and systemic administration of cortisone coincident with antibiotic therapy also was not effective. X-rays, in doses varying from 350 to 750 r, to the various lids had no effect. The base of the membrane was excised, and the defect covered by a fornix-based conjunctival flap, but the membranes recurred. Repeated cauterization with 1 to 3% silver nitrate did not slow the membrane formation, nor did desensitization to Streptococcus vaccine affect the disease. On a recent admission, it was found that a membrane could be induced to form in a previously uninvolved area by traumatizing the conjunctiva with forceps. The lesions have remained essentially unchanged to date.

CASE 2.—The younger brother was seen at the age of 3 months, with a history of red eyes for four days. Thick yellowish membranes covered the palpebral conjunctiva of all lids. The bulbar conjunctiva was not involved, and the corneas were clear. Ophthalmoscopic examination revealed nothing remarkable. Cultures yielded a heavy growth of Type VII Pneumococcus, which was sensitive to streptomycin, penicillin, oxytetracycline (terramycin®), and chloramphenicol (chloromycetin®). M. pyogenes var. albus, coagulase-negative, was also isolated. Tubercle bacilli, anaerobic bacilli, and fungi could not be identified on culture. Virus and rickettsial agents could not be isolated by mouse-brain or egg-membrane inoculation. Inoculation on rabbit corneas produced no pathologic lesion. Penicillin (300,000 units per day) was given systemically, and in two days the cultures were sterile but the membranes persisted. Penicillin was given for 22 days without altering the membranes. After two weeks local treatment with cortisone drops was begun, and two days later systemic administration of cortisone was started and continued for 11 days. During this time the membranes, though mechanically removed several times, returned. Local and systemic treatment with oxytetracycline was given for 16 days, with some diminution in the rapidity of the growth of the membranes in the left eye. The child was discharged under a regimen of instillation of cortisone drops and local applications of oxytetracycline ointment. One month later an exacerbation of the membranes occurred coincidentally with an infection of the upper respiratory tract. The left cornea was found to stain with fluorescein. Use of cortisone was discontinued, and sulfacetimide drops were given. The keratitis cleared, but the membranes persisted. On a recent admission it was found that a membrane could be induced to form in a previously uninvolved area by traumatizing the conjunctiva with carbon dioxide snow (dry ice).

SUMMARY AND CONCLUSIONS

Bacteriological studies in two cases of chronic membranous conjunctivitis in infant brothers revealed a number of organisms at various times, including hemolytic and nonhemolytic streptococci, Micrococcus pyogenes var. albus, and, more consistently, Type XIX and Type VII Pneumococcus. Special studies for tubercle bacilli, fungi, and viruses gave negative results. The conjunctiva was kept sterile by antibiotic treatment for a period of six weeks, in the first case, and of three weeks, in the second, without affecting the rate of formation of the membranes, although the condition was improved by the control of secondary infection. It was found possible to induce the formation of a membrane in a previously uninvolved area by traumatizing the conjunctiva, in the one case with forceps and in the other with carbon dioxide snow. These findings have led to the conclusion that the disease in these two cases is a primary tissue aberration in which the ordinary inflammatory reaction to bacterial agents or to trauma has been modified to run a more torpid course. The involved mucous membranes respond with a peculiar fibrinous exudate and the formation of chronic membranes on the palpebral conjunctiva.

COMPARISON OF LOCAL AND SYSTEMIC EXPOSURES IN PRODUCTION OF RADIATION CATARACT

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IT IS WELL known that cataract may result from exposure to ionizing radiations,[1] but the pathogenesis of the lesion is not fully understood. Since opacification of the lens is also produced by a variety of chemical, metabolic and endocrine disorders,[2] the biochemical disturbances resulting from whole-body irradiation [3] might be expected to contribute to cataractogenic effects. Were the lens injured indirectly in this way, the threshold cataract-inducing dose of radiation would depend in part upon the degree of general body damage, or upon the total volume of tissue irradiated. Likewise, some measure of protection against cataract formation might be afforded by shielding a part of the body or an organ, such as the spleen, which protects against other types of irradiation-induced injuries.

Because of current interest in the problem of radiation-induced cataract, experiments were undertaken to answer these questions. Groups of mice were given graded doses of x-radiation, the whole body, the head, or the body only being exposed, and the eyes of these animals were studied periodically thereafter with the slit lamp for cataract.

MATERIALS AND METHODS

Female Rf mice 7 to 9 weeks of age were exposed to 15 to 405 r of x-radiation, with the following factors: 250 kv (peak); 76 to 84 r per minute; 30 ma.; 3 mm. Al filtration; 37.9 cm. skin-target distance. The mice were held in position during exposure within perforated, thin-walled, lucite® tubes, in which they fitted snugly and could not move about freely. Shielding of the head or body was accomplished by interposing a layer of lead 6 mm. in thickness between the part to be shielded and the x-ray tube. The dose, delivered in a paraffin phantom positioned beneath the shield, was found to be approximately 2% of that outside the shielded area. After irradiation the animals were fed and caged under standard laboratory conditions. Periodically mice were chosen from each group and examined as unknowns with the Zeiss "opton" slit lamp for opacities of the lens. Lesions were graded + to ++++, as illustrated previously.[4] Grade + denotes the presence of small, subcapsular, dot-like opacities in the posterior polar region. These

From the Division of Biology, Oak Ridge National Laboratory.

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1. Cogan, D. G.: J. A. M. A. **142**:145, 1950.

2. Sommers, I. G.: Histology and Histopathology of the Eye and Its Adnexa, New York, Grune & Stratton, Inc., 1949, pp. 442-448.

3. Curtis, H. J.: Ann. Rev. Physiol. **13**:41, 1951.

4. Christenberry, K. W., and Furth, J.: Proc. Soc. Exper. Biol. & Med. **77**:559, 1951.

are usually clustered about the posterior suture and appear as an inverted Y-shaped lesion. In addition, there is a peripheral ring of similar opacities in the equatorial region. With progression to Grade ++ the opacities become denser and extend into the posterior cortex, with linear radiations toward the equator. With Grade +++ the radiating opacities form a sunburst pattern extending into the equator of the lens and around into the anterior cortex. Concomitantly, there is development of anterior polar and radiating subcapsular opacities of less severity. Nuclear involvement does not occur until the cortical lesions are far advanced. Total opacity is referred to as Grade ++++.

RESULTS

Opacities of the lens occurred at all dose levels but were not observed in the nonirradiated controls (Table). The cataracts made their appearance after a latent period which varied inversely with the dose of radiation, and they progressed in severity at a rate directly proportional to the dose. Thus, in the mice given 405 r opacities were first detected after 11 weeks and 25 weeks after irradiation had progressed in degree to Grade ++, while in the animals receiving 15 r opacities were still beginning to appear 33 weeks after exposure. Irradiation of the body

Relation of Cataract Formation to Dose of X-Radiation

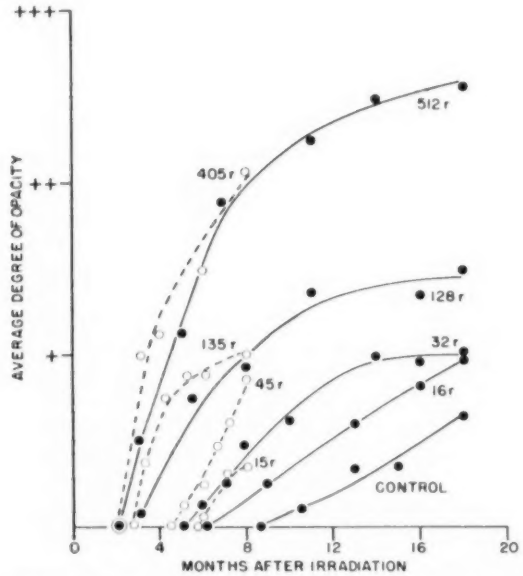
No. of Mice	Dose, r	Region Exposed	Average Latent Period, Wk.	No. Mice with Opacities 33 Wk. After Exposure		
				−	+	++
9	405	Total body	11	..	1	8
9	405	Head only	11	..	..	9
18	405	Body only	..	16	1 *	1 *
14	135	Total body	17	..	14	..
13	135	Head only	17	..	13	..
17	135	Body only	..	17	..	..
18	45	Total body	28	2	16	..
19	45	Head only	28	3	16	..
21	15	Total body	33+	14	6	1
17	15	Head only	33+	12	5	..
18	0	.....	..	18	..	..

* The isolated opacities in this group are attributed to imperfect shielding, due to movement of the mice during exposure, with resulting direct irradiation of the head.

alone, with the head shielded, did not produce cataract, except in 2 of the 18 mice given 405 r; in these cases the opacities are believed to represent imperfect shielding of the head, due to movement of the mice during irradiation. In view of experimental factors, such as scatter and the difficulty of immobilizing mice without anesthesia, it is surprising that not more of the head-shielded animals revealed evidence of faulty shielding. The time of onset, progression, configuration, and severity of opacities were approximately the same after irradiation of the head alone as after total-body exposure.

The opacities seen in these animals corresponded closely to those observed previously in mice of the same stock exposed to 16 to 512 r of x-radiation or to corresponding doses of thermal neutron-gamma radiation, described in a preliminary report.[4] In the earlier study, which is still in progress, mice were observed until natural death, and the progression of opacities was followed over a longer period than in the present experiment, which was terminated 33 weeks after exposure of the animals. The similarity of the time of onset, progression, and intensity of opacities in the two studies is indicated in the accompanying Chart. The slightly more rapid progression of opacities in the present series of mice, as compared with that of the

animals exposed previously, may be due to the higher dose rate (76 to 84 r per minute) in this study than in the former (6.4 r per minute). In each experiment, after doses of 400 r or more, opacities were present within 90 days and advanced relatively rapidly in severity, in the former study reaching Grade ++ to +++ at the end of 18 months. In contrast, after doses of 128 r or less the opacities were of later onset (four months or more after irradiation) and usually failed to progress to Grade ++, even in old age. With doses as low as 15 or 16 r opacities appeared 6 to 8 months after exposure and averaged Grade + in severity at the end of 18 months. Naturally occurring, senile opacities developed later in life (10 to 14 months) and remained statistically less numerous and less well advanced. Their appearance with the slit lamp resembles that of the early radiation-induced opaci-



Opacities of the lens in relation to dose of x-radiation and time after exposure. The open circles and interrupted lines indicate opacities in mice followed for eight months after irradiation. The solid circles and continuous lines denote opacities in mice irradiated earlier and observed throughout their life span.

ties; however, the senile changes are characterized by a more diffuse scattering of dot-like and vacuolar opacities in the cortex of the lens, as well as by accentuation of the lens nucleus. Complete opacities (Grade ++++) were not observed in the x-irradiated animals of either study but were encountered among mice of the earlier series surviving median-lethal (LD_{50}) doses of thermal neutron-gamma radiation; they have been noted also in mice of another strain exposed more recently to total-body fast neutron-gamma radiation, even with doses in the LD_{10} range. These findings are consistent with earlier observations indicating a high relative biologic effectiveness of neutron radiation in cataract induction.[5]

5. Christenberry and Furth.[4] Evans, T. C.: Radiology **50**:811, 1948.

COMMENT

While it is well recognized that local, or unilateral, irradiation of the eye produces cataract, the possibility of the existence of indirect cataractogenic effects, resulting from the massive irradiation of extraocular tissues, had not been explored previously.

From the present study it is concluded that cataract induction by irradiation depends upon exposure of the eye itself, since no cataractogenic effects were detected after exposure of the remainder of the body to a wide range of doses. It is probable, from evidence now available, that cataract results from radiation injury of the cells of the anterior epithelium of the lens.[6]

It is significant that the sensitivity of the lens to cataract induction is not increased with whole-body irradiation; in this respect the process differs from radiation injuries in general, such as damage to hemopoietic organs, epilation, and inhibition of antibody production. It is also clear from this study that protection against cataract formation is not conferred appreciably by shielding the extraocular tissues from radiation, even though all the body except the head is thus shielded. The existence of other mechanisms of protection is indicated by the protective effects conferred upon the lens by cysteine [6a]; however, an agent of practical value in preventing radiation-induced cataract is yet to be found.

SUMMARY

1. Opacities of the lens were readily induced in mice by x-radiation, the threshold dose being somewhat less than 15 r.

2. The opacities increased in severity with the dose and time after irradiation, the incidence of lesions approaching 100% at 33 weeks after exposure to doses of 45 r or more.

3. Cataract did not occur if the head was shielded from radiation, although the remainder of the body received doses as large as 405 r, a result supporting the view that cataract induction depends upon irradiation of the eye itself.

4. The induction time, progression, configuration, and severity of opacities were approximately the same after exposure of the head alone as after total-body irradiation, indicating that protection of the eyes against cataract is not afforded by shielding the remainder of the body.

6. (*a*) von Sallmann, L.: A. M. A. Arch. Ophth. **47**:305, 1952. (*b*) Cogan, D. G.; Goff, J. L., and Graves, E.: Ibid **47**:584, 1952.

ROLE OF CORTISONE IN GLAUCOMA SURGERY

Experimental Results

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THE GOAL of all types of surgery employing an iris-inclusion or a trephine technique is to establish a permanent patent fistula from the anterior chamber to the subconjunctival spaces. However, the fundamental drawback of all such operations has been the too frequent failure of these artificially created channels to remain patent; in too many cases the pathways so created are obliterated when the normal process of wound healing occurs. Any process or drug which could delay fibrous tissue formation would be a boon indeed to the ophthalmic surgeon practicing glaucoma surgery.

In 1950 Ragan and associates,[1] while working on rabbits, demonstrated that cortisone had the ability to delay wound healing. Spain and associates,[2] employing mice, came to the same conclusion, stating: "Unquestionably, cortisone inhibits the formation of granulation tissue. . . . The effect is rapid and of short duration." Spain and his co-workers also found that cortisone was effective in decreasing fibrosis only when it was employed early in the process of wound healing and that it had no appreciable effect upon already existing granulation tissue. Leopold and co-workers [3] mentioned a decrease in the amount of healing in the rabbit's sclera and epithelium when frequent topical administration of cortisone was employed.

PURPOSE OF INVESTIGATION

It was not long before this encouraging bit of information was utilized by one of us (J. L.) in glaucoma surgery. According to this procedure, 24 hours before an operation oral administration of cortisone is started; 25 mg. is administered every four hours around the clock. This dosage is continued for the first seven days after operation, and the dose is then reduced to 25 mg. four times a day for the second postoperative week. During the third week the dose is reduced to 25 mg. three

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1. Ragan, C.; Howes, E. L.; Plotz, C.; Meyer, K., and Blunt, J. W.: Effect of Cortisone on Production of Granulation Tissue in the Rabbit, Proc. Soc. Exper. Biol. & Med. **72**:718 (Dec.) 1949. Creditor, M. C.; Bevans, M.; Mundy, W. L., and Ragan, C.: Effect of ACTH on Wound Healing in Humans, ibid. **74**:245 (May) 1950. Howes, E. L.; Plotz, C.; Blunt, J. W., and Ragan, C.: Retardation of Wound Healing by Cortisone, Surgery **28**:177 (Aug.) 1950.

2. Spain, D. M.; Molomut, N., and Haber, A.: Biological Studies on Cortisone in Mice, Science **112**:335 (Sept. 22) 1950.

3. Leopold, I. H.; Purnell, J. E.; Cannon, E.; Steinmetz, C., and McDonald, P. R.: Local and Systemic Cortisone in Ocular Disease, Am. J. Ophth. **34**:361 (March) 1951.

times a day; thereafter, cortisone (cortone®) acetate drops (5%) are instilled daily every three hours for one week and then three times a day for two weeks. However, we were of the opinion that a controlled experiment to determine the validity of this concept was indicated. The purpose of this experiment was to discover just what effect cortisone would have in laboratory animals upon the healing of scleral wounds similar to those employed in glaucoma surgery. It was felt that if cortisone administered subconjunctivally caused a marked delaying action in fibrous tissue formation, it would then be possible to envisage its administration as a routine procedure in all glaucoma operations in which drainage is desired. The subconjunctival route of administration was chosen because (1) the systemic effects of the drug are eliminated or reduced to a negligible amount; (2) it is desirable to leave the eye bandaged for five days after operation, except for daily dressings, thus rendering

TABLE 1.—*Data on Control for Experiments 1 and 2*

Animals		Type of Surgery	Interval Before Killing	Degree of Healing
750	OD	Keratome section	1 wk.	Well healed
	OS			
571 *	OD	Trephination	4 days	Well healed
	OS	Discarded		
577 *	OD	Trephination	4 days	Fairly well healed
	OS			
812 *	OD	Discarded		
	OS	Trephination	1 wk.	Fairly well healed
867 *	OD	Trephination	1 wk.	.....
	OS			
441	OD	Keratome section	2 wk.	Well healed
	OS			
561 *	OD	Trephination	2 wk.	Well healed
	OS			
805 *	OD	Trephination	2 wk.	Well healed
	OS			
811 *	OD			
	OS	Trephination	2 wk.	Well healed
765	OD	Keratome section	3 wk.	Very well healed
	OS	Discarded		
933	OD	Trephination	3 wk.	Very well healed
	OS	Discarded		
615	OD	Discarded		
	OS	Trephination	3 wk.	Very well healed
766	OD	Trephination	3 wk.	Very well healed
	OS	Keratome section	3 wk.	Very well healed

* Controls in Experiment 2.

impractical repeated topical applications; (3) the highest concentration would be achieved at the desired site, or relatively close to it.

However, as our work proceeded, it became apparent that the intramuscular route of administration was perhaps a better one, and therefore we extended the original scope of the experiment to include a series in which the intramuscular route of cortisone administration was used.

PROCEDURE

For the three experiments in this project a total of 49 rabbits between the ages of 3 and 6 months were employed. The animals were divided originally into two equal groups—one to serve as the control group and the other as the cortisone-treated group. Except that the rabbits in the second group received cortisone, there was no deviation in the treatment of the animals at any stage of the experiment. However, as we varied the rates and times of administration of cortisone subconjunctivally, we decreased the number of controls, since the original control animals were adequate for the second experiment. Hence, in our table of controls (Table 1) it

will be noted that controls from Experiments 1 and 2 are used interchangeably. However, in Experiment 3, in which we varied our surgical technique, we established an entirely new and equal set of controls to conform to the new surgical method. Three methods of administering the cortisone were employed.

EXPERIMENT 1.—In this experiment the animals received 0.5 cc. of cortisone acetate solution, equivalent to 12.5 mg. of cortisone, injected subconjunctivally opposite the operative site at the time of operation and once a week thereafter. At the end of one week it was found that a large deposit from the previous injection remained.

EXPERIMENT 2.—This experiment differed from the first only in that the cortisone solution (0.5 cc.) was administered subconjunctivally 24 hours prior to operation and thereafter 0.5 cc. of cortisone was given subconjunctivally every other day, despite the presence of large, unabsorbed deposits.

EXPERIMENT 3.—In this experiment the animals were given intramuscular injections of cortisone daily for three days prior to operation and every day thereafter until they were killed. The cortisone was administered to them on the basis of 1 mg. of cortisone per pound (2 mg. per kilogram) of body weight.

Originally the experiments were conducted under absolutely sterile conditions. Thus, all the animals in Experiment 1 received mild silver protein N.F. (20%) in the conjunctival sac prior to operation, and the surgeons wore masks, caps, and gowns. However, we soon found this to be unnecessary, and the elaborate procedure was abandoned, with no resulting cases of infection. The copious use of intramuscular injections of penicillin, plus the resistance to infection of laboratory animals, is apparently enough to prevent bacterial infection in rabbits.

All the rabbits received topical anesthesia, induced with 2% tetracaine hydrochloride, and general anesthesia, induced with pentobarbital sodium given intravenously, in a dose of 6 mg. per kilogram of body weight.

The surgical technique employed in Experiments 1 and 2 was as follows: A large conjunctival flap was made beneath the nictitating membrane, and the capsule of Tenon was dissected down to the sclera and then cleared to the limbus. At this point either a keratome section or a through-and-through 2-mm. trephine opening was made down to uveal tissue, allowing aqueous to escape, and thus indicating that the anterior chamber had been entered. The conjunctiva was then sewed together with a continuous 6-0 nonabsorbable surgical (black silk) suture. The rabbits in the experimental group then received their cortisone subconjunctivally at the opposite pole. Each animal received 300,000 units of procaine penicillin G intramuscularly, and penicillin ointment was instilled into the cul-de-sac. Thereafter, each animal received 150,000 units of procaine penicillin G daily intramuscularly.

In Experiment 1 either keratome or trephine incisions were employed, and in Experiment 2 trephination alone was performed. The technique for Experiment 3 was altered considerably and consisted in the following procedure: The conjunctival flap was made as previously described, but the trephine incision, instead of being placed at the limbus, was placed 5 to 10 mm. behind the limbus, in the sclera. The trephine incisions were not of the full penetrating type; lamellar trephine incisions, passing through the greater thickness of the sclera, were considered adequate. This new method did not involve entering the anterior chamber at any time during the operation. Because of the entirely new technique, a new and equal number of controls were established to conform to the cortisone-treated animals.

All the animals which were treated with cortisone by any of the three methods were killed at the end of four days, one week, two weeks, three weeks, or four weeks. The eyes were then enucleated, fixed in Bouin's solution and alcohol, blocked in paraffin, sectioned serially, stained with hematoxylin and eosin, and studied.

RESULTS

A total of 98 rabbit eyes were employed for this investigation: 30 in Group 1; 32 in Group 2, and 36 in Group 3. Of this total, it was necessary to discard two eyes from Group 1, six eyes from Group 2, and three eyes from Group 3, for technical reasons. The results obtained in the three groups were as follows:

EXPERIMENT 1.—In this group a total of 24 eyes were available for study and evaluation. Table 1 lists the types of surgery performed, the time at which the animals were killed, and the results obtained for the control group of animals. In Table 2 the same information is found for the group treated with cortisone. From this table it is apparent that, except in the first week, there was no major change in the pattern of healing which occurred in the control and in the experimental group, except perhaps for a slight lag in the treated animals. Examination of the serially sectioned slides at the end of the second and third postoperative weeks revealed perhaps a slight decrease in the staining qualities of tissues in the treated group. Otherwise, the rate and the type of healing in the two groups were fairly uniform.

Perhaps one could say that in some of the slides there was a slightly less dense cellular matrix in the treated group. However, this difference was so slight as to

TABLE 2.—*Data on Animals Treated with Cortisone in Experiment 1*

Animals		Type of Surgery	Interval Before Killing	Degree of Healing
700	OD	Keratome section	1 wk.	Poor healing
	OS			
718	OD	Trephination	1 wk.	Fair healing
	OS			
725	OD	Trephination	1 wk.	Good healing
	OS			
679	OD	Keratome section	2 wk.	Good healing
	OS			
567	OD	Trephination	2 wk.	Good healing
	OS			
916	OD	Discarded		
	OS	Trephination	3 wk.	Good healing
743	OD	Discarded		
	OS	Keratome section	3 wk.	Good healing
747	OD	Trephination	3 wk.	Good healing
	OS	Discarded		
609	OD	Trephination	3 wk.	
	OS	Trephination	3 wk.	Good healing

be of no clinical significance, the essential element being that the surgically created wound had been solidly bridged over by proliferation of new fibrous tissue. This held equally well for the keratome and for the trephine sections. The size of the trephine opening as compared with the keratome section had no apparent influence on the degree of fibrosis which occurred. It was abundant in both instances. Study of the slides revealed complete filling of the surgically created wounds by fibroblasts, which, with minor variations, were closely packed by the third week. The fibroblasts spanned the wound, following the direction of the scleral lamellae. The growth was so profuse that it was difficult to determine whether the wounds had healed from above or from below. Photomicrographs taken of both control and experimental eyes reveal the following points: Figures 1 *1* and 2 *1* represent eyes from the control group, killed two and three weeks, respectively, after operation. Figures 1 *2* and 2 *2* were taken from animals treated with cortisone and killed two and three weeks respectively, after operation. No apparent difference is to be noted in the four slides other than perhaps a slighter staining quality of the fibroblasts spanning the keratome sections in the cortisone-treated eyes. These slides are typical of the results which were obtained throughout in the second and third weeks.

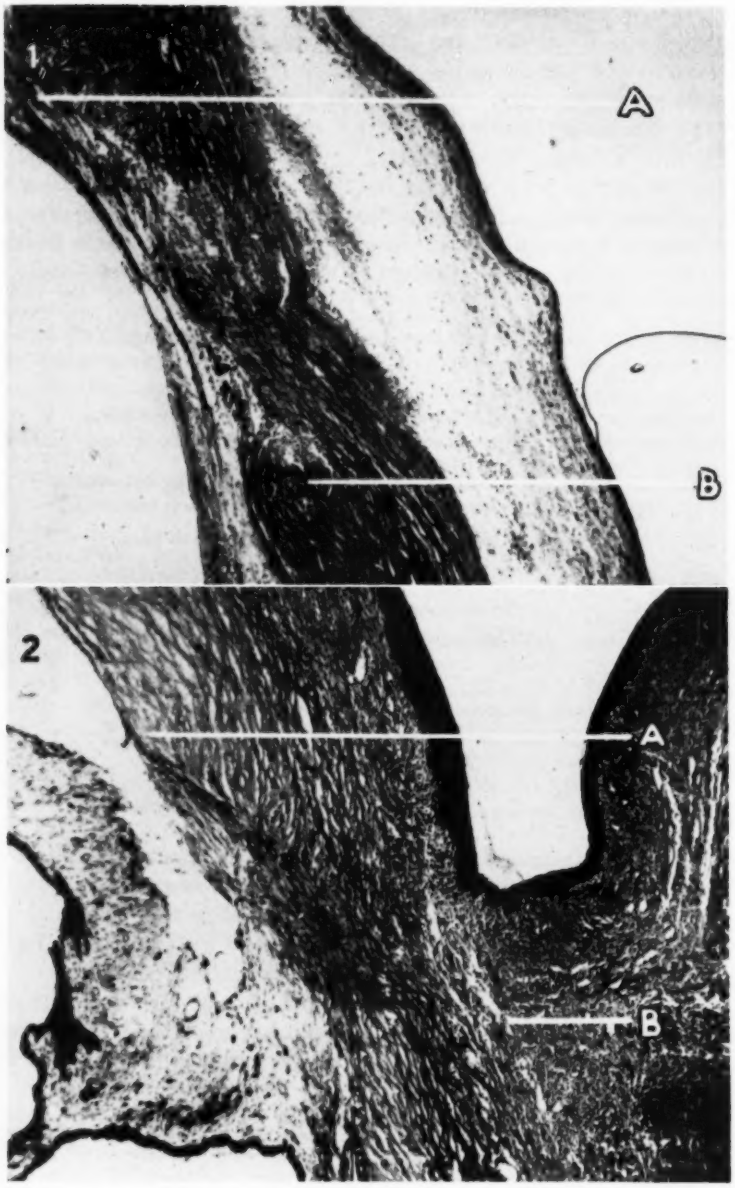

Fig. 1.—*1* (Eye 441, O.D.), control eye two weeks after a keratome section below the ciliary body. The area between *A* and *B* indicates the degree of fibrosis which had taken place.

2 (Eye 679, O.D.), treated eye at the end of two weeks. A keratome section, as denoted by the lines *A* and *B* was made two weeks before, and at the time the animal was killed the area was completely covered by new connective tissue.

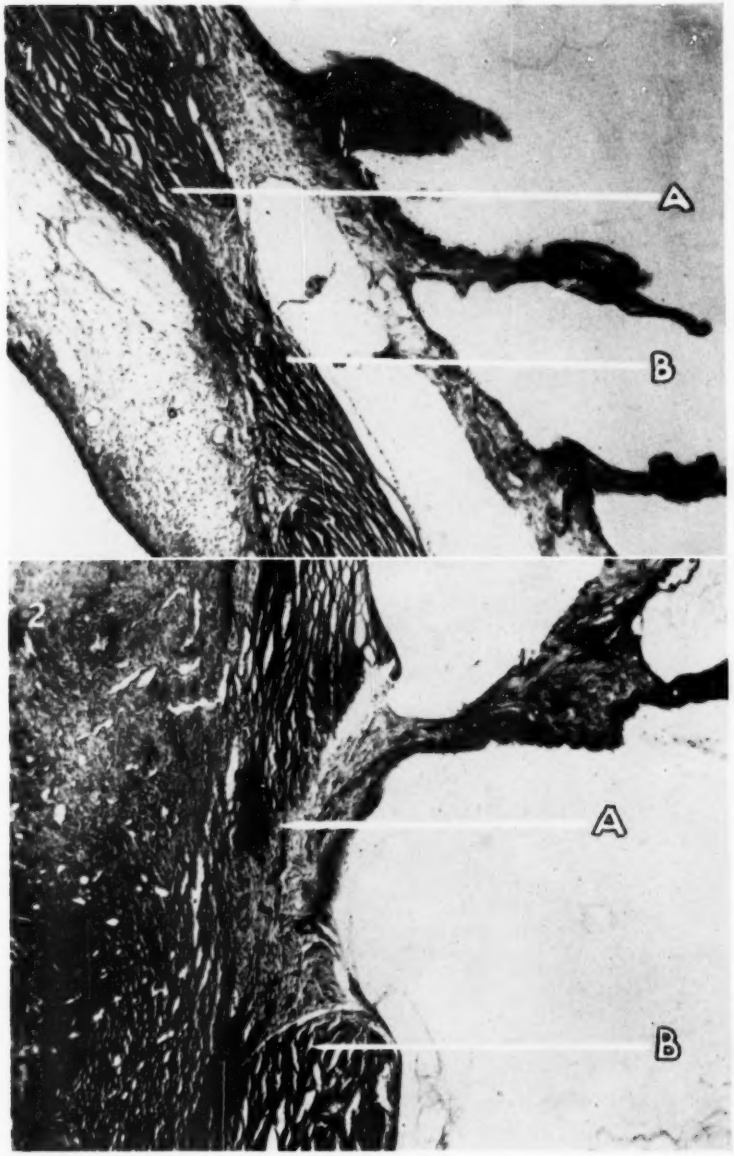

Fig. 2.—*1* (Eye 765, O.D.), control eye of rabbit killed three weeks after a keratome section had been made at the root of the iris. The area between lines *A* and *B* represents dense and profuse healing and fibrous tissue formation.

2 (Eye 743, O.S.), cortisone-treated eye at the end of three weeks' treatment. The area between *A* and *B* represents the well-healed keratome section at the root of the iris.

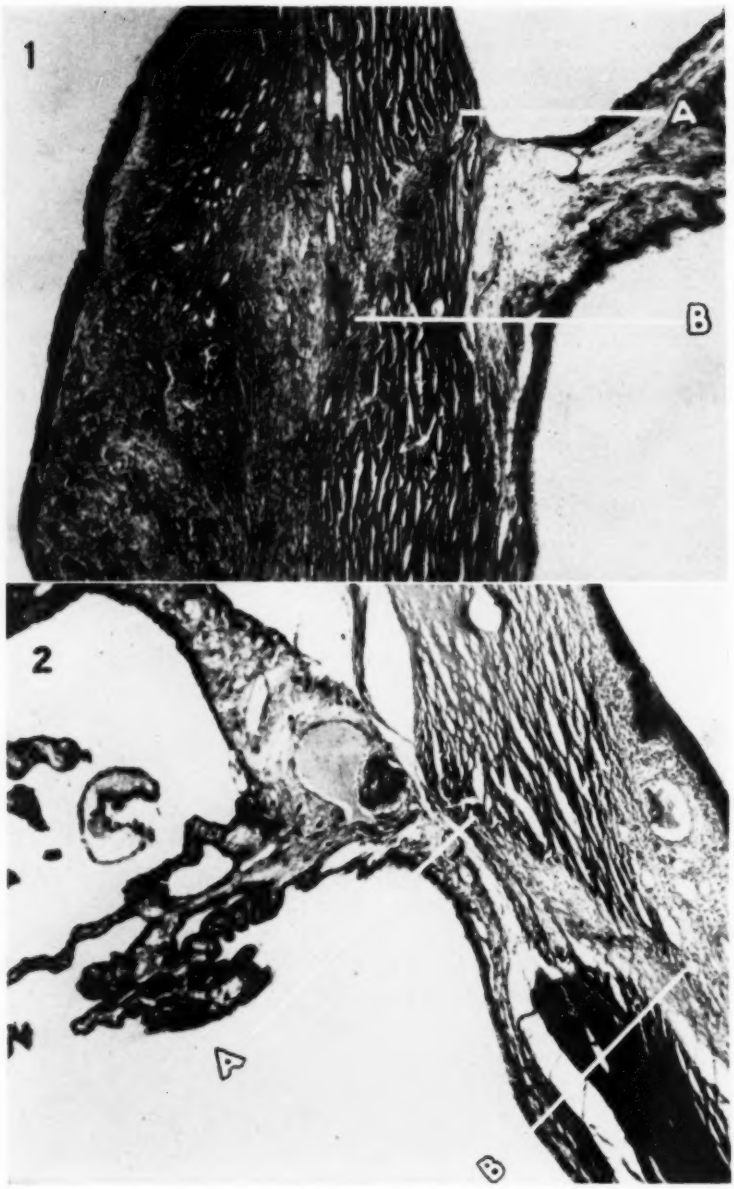

Fig. 3.—*1* (Eye 750, O.D.), control eye of animal killed at the end of one week. This eye had a keratome section in the area indicated by the lines *A* and *B*. The section had abundantly healed through the formation of new fibrous tissue, as indicated.

2 (Eye 700, O.S.), cortisone-treated eye at the end of one week's treatment. The area between lines *A* and *B* represents the healing process that followed a keratome incision through the sclera at the base of the iris.

The picture found in the eyes of animals killed at the end of one week was somewhat different. In this group a total of six eyes were treated with cortisone. Examination of Figure 3 *1* and *2*, representing respectively, the control and experimental eyes at the end of one week, reveals a discernible difference; fibrous tissue proliferation in Figure 3 *1* is denser, closer packed, and stains much more heavily than it does in Figure 3 *2*. The looseness with which the fibroblasts have filled in the wound in Figure 3 *2* is very apparent and stands out in strong contrast to the density in the control eye (Fig. 3 *1*).

Thus, from the experiments in Group 1, it can be concluded that there was an initial deceleration in the process of healing in those eyes that were treated weekly with subconjunctival injections of cortisone. However, this depression of mesenchymal activity was minimal and not clinically significant. This depression was most apparent at the end of one week. At three weeks the only remaining traces of it that could be found consisted in the slightly lighter-staining qualities of the new fibrous

TABLE 3.—*Data on Animals Treated with Cortisone in Experiment 2*

Animal		Type of Surgery	Interval Before Killing, Days	Degree of Healing
566	OD	Trephination	4	Fair healing
	OS			
38	OD	Trephination	4	Well healed
	OS			
801	OD	Trephination	7	Well healed
	OS			
597	OD	Trephination	7	Well healed
	OS			
565	OD	Trephination	7	Fairly well healed
	OS			
814	OD	Trephination	14	Well healed
	OS			
802	OD			
	OS	Trephination	14	Well healed
567	OD			
	OS	Trephination	14	Well healed
803	OD			
	OS	Trephination	14	Well healed

tissue in the cortisone-treated eyes. The effect of weekly subconjunctival administration of cortisone was that of a transient and minimal depression, which was no longer apparent by the end of the third week.

EXPERIMENT 2.—All the animals employed in the second part of this experiment had trephinations (2 mm.) performed. The data on the controls are listed in Table 1, and the data on the treated animals are tabulated in Table 3.

Of this group, which had subconjunctival injection of cortisone prior to operation and daily thereafter, four eyes at the end of 4 days of treatment, six eyes at the end of 7 days of treatment, and eight eyes at the end of 14 days of treatment with cortisone showed the same results as those described in Experiment 1.

With the exception of two eyes in the cortisone-treated group examined at the end of four days (from two different animals), the picture of the fibrosis which had occurred was essentially the same. The fibrosis in the animals treated with cortisone subconjunctivally was as heavy, as thick, and as deep-staining at it was in the control group. Except for the slight transient depression in fibrosis found in the two eyes, all the other eyes revealed healing comparable to the stage at which the

animal was killed. Figure 4 shows the result in a treated eye from an animal killed at the end of the four-day period. We felt it was not necessary to present photomicrographs at subsequent periods, since the pictures were similar to those in Experiment 1. The same control pictures are valid here, although it will be seen from Table 1 that there were 14 new control eyes in the second experimental group.

EXPERIMENT 3.—In this group of animals treated intramuscularly with cortisone, there were a total of 16 treated eyes and 20 controls, of which 3 control eyes had to be discarded, for technical reasons. In all these animals a new procedure was employed, and therefore new controls were necessary. The results for this group of animals, both control and treated, can be found in Table 4.

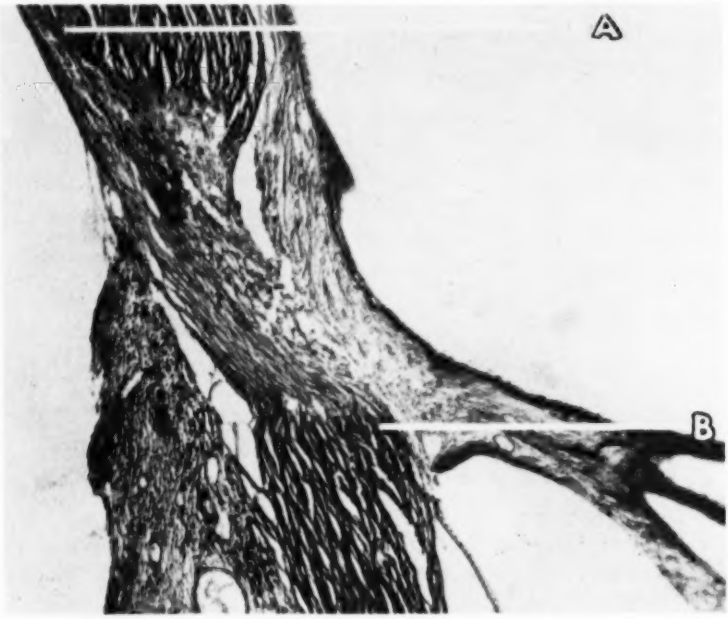

Fig. 4 (Eye 38, O.D.).—Cortisone-treated eye from Experiment 2 at the end of four days. The area between *A* and *B* indicates the degree of healing that had taken place.

For the purpose of ease and clarity in presenting the results in this experiment, we have not employed the same terms as those in Experiments 1 and 2 in evaluating our results; rather, because of the marked differences in the degree of healing, we have resorted to an arbitrary classification, as follows: — indicates no fibroblastic proliferation; +, an occasional fibroblast present in the trephine wound; ++, strands of fibroblastic proliferation present, but not quite bridging the wound, and thin in degree; +++, fibroblastic proliferation that completely covers the wound from edge to edge.

Examination of the slides from the cortisone-treated animals revealed a striking depression of the mesenchymal activity that was so prominent in Experiments 1 and

2. Here, examination of slide after slide revealed almost total absence of fibroblastic proliferation. As can be seen in Table 4 B, there were eyes at the end of 26 days of treatment which still lacked any fibrous tissue formation. There was a total depression of all fibroblastic activity, and no signs of new healing could be discerned in any of the slides. In many of them a thin line of stromal tissue bridged the trephine gap, as shown in Figure 5, with total absence of fibroblastic repair. It would seem that the mesenchymal element had been completely halted in its efforts at proliferation.

TABLE 4.—*Data on Experiment 4*

Animals		Type of Surgery	Interval Before Killing, Days	Degree of Healing	
		A. Controls for Experiment 3			
229	OD	Partial Trephine Incision	7	OD	—
	OS	Through Sclera		OS	+
132	OD	Partial Trephine Incision	7	OD	+
	OS	Through Sclera		OS	+
226	OD	Partial Trephine Incision	7	OD	+
	OS	Through Sclera		OS	++
424	OD	Partial Trephine Incision	15	OD	+++
	OS	Through Sclera		OS	Discarded
895	OD	Partial Trephine Incision	15	OD	Discarded
	OS	Through Sclera		OS	+++
91	OD	Partial Trephine Incision	15	OD	Discarded
	OS	Through Sclera		OS	+++
41	OD	Partial Trephine Incision	27	OD	+++
	OS	Through Sclera		OS	±
53	OD	Partial Trephine Incision	27	OD	+++
	OS	Through Sclera		OS	+++
66	OD	Partial Trephine Incision	27	OD	+++
	OS	Through Sclera		OS	+++
69	OD	Partial Trephine Incision	27	OD	+++
	OS	Through Sclera		OS	++
		B. Treated with Cortisone in Experiment 3			
884	OD	Partial Trephine Section	7	OD	—
	OS			OS	+
880	OD	Partial Trephine Section	7	OD	+
	OS			OS	—
882	OD	Partial Trephine Section	7	OD	—
	OS			OS	—
893	OD	Partial Trephine Section	15	OD	+
	OS			OS	++
881	OD	Partial Trephine Section	15	OD	—
	OS			OS	+
359	OD	Partial Trephine Section	26	OD	+
	OS			OS	+
227	OD	Partial Trephine Section	26	OD	++
	OS			OS	—
59	OD	Partial Trephine Section	26	OD	+
	OS			OS	++

One saw only the bare cut ends of the sclera. Figure 5 presents an eye that was treated with cortisone and the animal killed at the end of 15 days. Figure 6 shows the cortisone-treated eye of a rabbit killed at the end of one week. The thin line of connective tissue which bridges these gaps is clearly visible, as is the total absence of any cellular proliferation. By way of contrast, Figures 7 and 8 represent eyes from control animals killed at the end of one and two weeks, respectively. The difference between these figures is so striking and so significant that comment is hardly necessary. The new fibroblastic proliferation seems to arise from both conjunctival

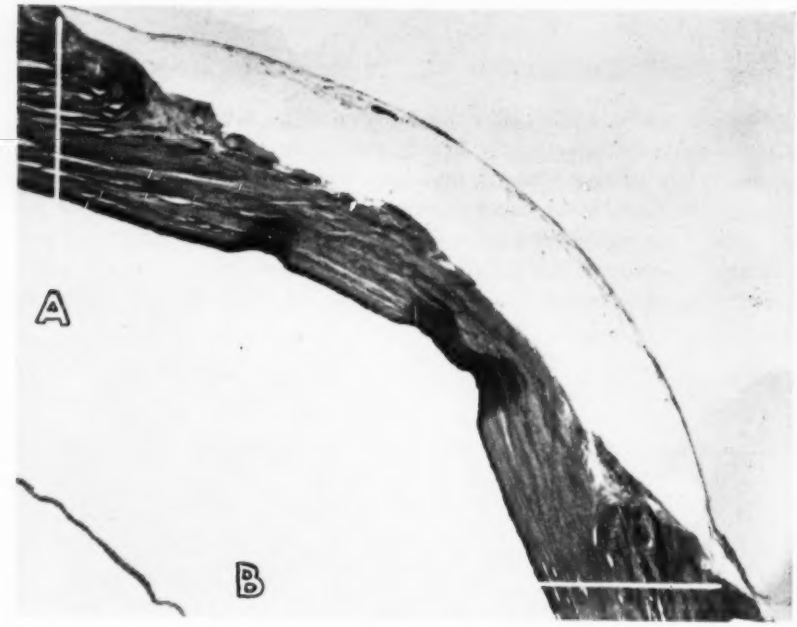

Fig. 5 (Eye 893, O.D.).—Lamellar trephine incision in the sclera of a cortisone-treated eye at the end of 15 days. Note the absence of fibroblasts in the trephine area, which is covered over by a thin layer of mesenchymal tissue.

Fig. 6 (Eye 884, O.D.).—Partial trephine incision through the sclera in a cortisone-treated eye at the end of one week. Note failure of granulation tissue to invade the trephine area.

Fig. 7 Eye 226, O.D.).—Fibrosis at the end of one week in the wound created by a partial trephine incision of the sclera in a control.

Fig. 8 (Eye 895, O.S.).—Fibrosis at the end of two weeks in a partial trephine incision of the sclera in an animal used as a control.

and scleral elements in this instance. Figure 9 is from a cortisone-treated eye enucleated at the end of 26 days. It is apparent that the degree of fibrosis is still minimal. We found that there was some increase in the degree of fibrosis under cortisone therapy when the experiment was prolonged. However, this increase did not keep pace with the changes noted in the untreated group of animals. In all the treated animals the fibroblastic proliferation was minimal and had done little to occlude the rather large lumen of the wound.

SUMMARY AND CONCLUSIONS

Experiments were undertaken to determine the effect of cortisone given subconjunctivally and systemically on scleral healing.

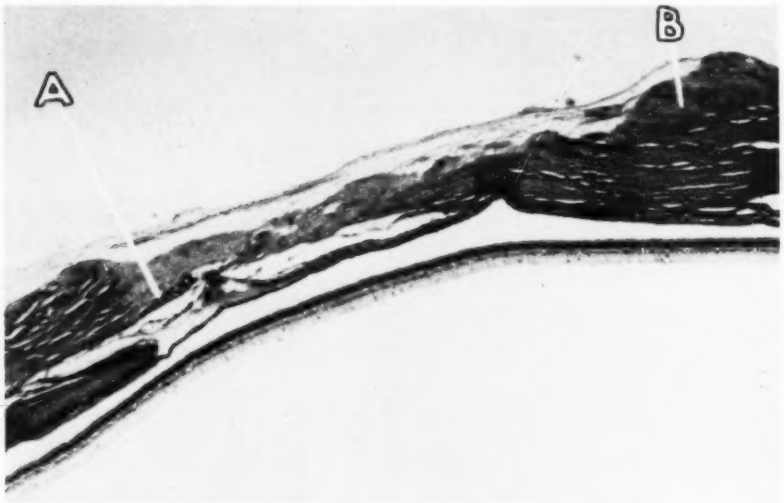

Fig. 9 (Eye 227, O.D.).—Minimal degree of fibroblastic proliferation in the partial penetrating trephine wound in the sclera of a cortisone-treated animal at the end of 26 days.

The results of the investigation suggest that cortisone administered subconjunctivally after glaucoma surgery in the rabbit has no effect in decreasing the amount of granulation tissue which forms or the degree of fibrosis which takes place. While there was some evidence that there was a transient and erratic initial deceleration in the healing process in an occasional rabbit, this was not very convincing. Fibrosis eventually takes place, nullifying any early effect of cortisone.

When we initially evaluated the results obtained in the rabbits employed in Experiment 1, we believed that our disappointing results (disappointing in terms of retarded healing) could be attributed to inadequate doses of cortisone administered too late to influence the course of scleral healing. In order to test this hypothesis, we undertook Experiment 2, whereby the administration of cortisone was begun prior to operation and maintained after operation in high dosage.

However, in Experiment 2 we found that the degree of fibrosis which occurred was only slightly and transiently depressed as compared with that in the controls.

We thus came to the conclusion that, regardless of the amount of cortisone administered subconjunctivally or the frequency of administration, there is proliferation attendant upon all healing processes which take place in the rabbit's sclera. Fibrosis nullifies any possible early effect of cortisone given subconjunctivally.

In Experiment 3 we had extremely gratifying results, and here we found that the findings were essentially a confirmation of those previously described by Ragan and by Spain and their co-workers. In our opinion, the changes which result from the subconjunctival administration of cortisone are transient and not very significant. However, those changes that result from the intramuscular administration are striking. This experiment would seem to prove that the intramuscular route of administration is the one of choice if the postoperative inhibition of fibrous tissue proliferation is to take place.

At present we are undertaking, on a large scale, a series of experiments to determine for what period of time fibrosis will be inhibited after the cessation of cortisone given intramuscularly and its effect upon actual iridencleisis and trephine operations over various periods. Of course, in actual clinical practice, the cortisone can be given by mouth or by intramuscular injection.

The results indicate that the subconjunctival administration of cortisone produces minor and transient depression of scleral healing. Systemic use of cortisone results in a remarkable delay in scleral healing and inhibits new fibroblastic activity.

Dr. William Toll helped with some of the rabbit surgery.

Mrs. Sylvia Richardson did the technical preparation of rabbit eyes for microscopic study.

MANAGEMENT OF OBSTRUCTIONS OF THE LACRIMAL CANALICULI WITH POLYETHYLENE TUBES

A Follow-Up Study

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IN A PREVIOUS article [1] a method of correction of strictures of the lacrimal canaliculi with polyethylene tubing was described and the possible use of this plastic material in restoration of the patency of lacrimal canaliculi destroyed by injury or disease was considered. Other investigators [2] have been interested in this field and have used tubes or rods of plastic material for the restoration of occluded or stenosed lacrimal canaliculi and nasolacrimal ducts.

In the evaluation of any new method it is the passage of time that best permits judgment as to the permanent effectiveness of any given procedure. With this in mind, I contacted my patients in whom a lacrimal canaliculus had been reconstructed by insertion of a polyethylene tube. Accurate follow-up data were obtained on five of these patients. In this series, the longest interval that has passed since the procedure was performed was 38 months, and the shortest follow-up period was 14 months.

REPORT OF CASES

CASE 1 (previously reported [1]).—A woman aged 21 had had continuous epiphora and intermittent dacryocystitis for seven years. At one time a "string" had been threaded through the lacrimal drainage passages into the nose. The string was removed after 10 weeks, but symptoms recurred. The right nasolacrimal duct and the right lower lacrimal canaliculus at its junction with the lacrimal sac were found to be occluded.

In April, 1949, dacryocystorhinostomy was performed and polyethylene tubing was inserted into the right lower lacrimal canaliculus. One end of the tubing was allowed to project from the lacrimal punctum and was taped to the cheek. To prevent extrusion, the tubing was sutured to the lining of the lacrimal canaliculus with one cotton suture. The tubing and suture were removed 46 days later.

It is now 38 months since the procedure was carried out, and there has been no recurrence of symptoms. The lacrimal canaliculus irrigates easily; the passage established by dacryocystorhinostomy remains patent, and there is no tearing in cold weather.

CASE 2.—A woman aged 41 had had roentgen therapy one year previously for a skin cancer occurring near the inner corner of the right eye. This treatment was soon followed by epi-

1. Henderson, J. W.: Management of Strictures of the Lacrimal Canaliculi with Polyethylene Tubes, Arch. Ophth. **44**:198-203 (Aug.) 1950.

2. Veirs, E. R.: Surgical Treatment of Lacrimal Drainage System, Texas J. Med. **46**:111-112 (Feb.) 1950; Nonsurgical Repair of Strictures of the Lacrimal Drainage System, A. M. A. Arch. Ophth. **47**:71-75 (Jan.) 1952. Callahan, A.: Surgery of the Eye: Injuries, Springfield, Ill., Charles C Thomas, Publisher, 1950, pp. 79-80. Scharf, J.: Über ein Verfahren der Rekanalisierung des Tränennasenkanals mit Einpflanzung eines Supramidröhrchens, von Graefes Arch. Ophth. **150**:678-682 (Sept.) 1950.

phora. Stenosis of the right upper and lower canaliculi was found near their junction with the lacrimal sac. The stenosis was of such a degree that it was difficult to force a No. 1 Bowman probe into the lacrimal sac. The right nasolacrimal duct was occluded.

In August, 1949, dacryocystorhinostomy was performed and polyethylene tubing was inserted through the right lower lacrimal canaliculus into the lacrimal sac, as in Case 1. The tubing was pulled out accidentally by the patient on the day after operation and had to be reinserted.

Ten days later the tubing was removed. Epiphora recurred within several months. Reexamination after 34 months showed that the lower canaliculus was still stenosed. The drainage passage into the nose established at operation, however, was patent, as demonstrated by the flow of fluid into the nose when the stenosed passage was forced with a lacrimal cannula.

CASE 3.—Two and a half years prior to examination a girl, 6 years of age, had been attacked by a dog, with a resultant laceration of the left lower eyelid and a broken nose. Epiphora of the left eye had been present since this injury.

Almost the entire length of the left lower canaliculus was found to be occluded by scar tissue. The punctum could still be identified, but it was impossible to pass a probe through the punctum into the canaliculus.

In March, 1950, dacryocystorhinostomy was performed. In addition, a new lacrimal canaliculus was created. A sharp needle was passed from the lacrimal punctum into the lacrimal sac to dilate the passage, and then a piece of polyethylene tubing was threaded along the channel. The lateral end of the tubing was not anchored to the cheek by "Scotch tape," as in the previous cases, but was cut off so that the end would be flush with the surface of the punctum.

The tubing remained in position for 44 days and then was removed. Epiphora did not recur. Two years later the lacrimal canaliculus and the stoma between the lacrimal sac and the nose were still patent.

CASE 4.—A woman, aged 33, six and a half years before examination at the Mayo Clinic had had the upper and lower canaliculi on each side sealed by surgical diathermy used in the treatment of keratitis sicca. In the interval since this operation the flow of tears from each eye had increased gradually until the epiphora reached such a degree that the patient sought relief.

On examination of the eyelids all lacrimal canaliculi were found to be occluded. On the left side the lower lacrimal punctum could still be identified, but on the right side it was obliterated.

In March, 1951, a new lower canaliculus on the left side was created by forceful passage of needles and probes of increasing diameter through the lacrimal punctum. A polyethylene tube was then threaded along the passage thus created. The lateral end of the tubing was cut flush with the punctum so that it would not protrude. Dacryocystorhinostomy was not performed. On the right side a similar procedure was performed, and a new punctum was created.

The polyethylene tubing was left in place for 130 days, without significant tissue reaction. The right lower lacrimal punctum gradually sealed shut over the lateral end of the tube, and it was necessary to reopen the punctum to remove the tube from the canaliculus. On the left side the tubing was simply removed through the punctum. The new passages were then irrigated, but fluid did not pass into the nose because the nasolacrimal ducts were occluded. The canaliculi gradually closed off, and within a month tearing was nearly as abundant as before the operation.

CASE 5.—A woman aged 34 had had recurrent swelling and pain near the inner canthus of the right eye for approximately one year. She had undergone about 23 "probings" in a period of seven months as treatment for the inflammation. On pressure over the lacrimal fossa, mucoid material regurgitated into the conjunctival sac through the right upper canaliculus. The right lower canaliculus was found to be obstructed near its juncture with the lacrimal sac.

In April, 1951, dacryocystorhinostomy was performed and a polyethylene tube was inserted through the obstruction of the right lower lacrimal canaliculus. The lateral end of the tube was cut flush with the punctum and was sutured to the wall of the canaliculus with one cotton suture.

The cotton suture and tube were removed after 36 days, when the passages were patent into the nose. Fourteen months have now passed since operation, and there has been no recurrence of epiphora.

COMMENT

Certain features and observations made in the management of these five patients are worthy of comment. The most successful results occurred in those cases in which reconstruction of the canaliculus was combined with dacryocystorhinostomy. My experience indicates that stenosed or obstructed canaliculi usually are associated with some degree of occlusion of the nasolacrimal ducts. It would seem best, therefore, to assure an opening for the lacrimal drainage into the nose at the time the canaliculi are reconstructed. Had this been done in Case 4, it is possible that the canaliculi would have remained patent after removal of the polyethylene tubing.

In the first case in which this method of reconstruction of the lacrimal canaliculi was attempted, it was deemed advisable to tape the lateral end of the tubing to the face. This resulted in slight eversion of the eyelid and was of some annoyance to the patient while the tubing was in place. Subsequent experience has proved that it is just as practical to cut the tubing flush with the lacrimal punctum except in those cases in which the lacrimal puncta must be reconstructed also. In the latter cases it seems best to allow the tubing to protrude through the punctum in order to prevent stenosis at this point. Had this been done on the right side in Case 4, the punctum probably would not have sealed shut over the tip of the tube.

In the cases in which the lacrimal canaliculi remained patent after removal of the polyethylene tubing, the tubing was allowed to remain in the canaliculi for 46, 44, and 36 days, respectively. In a case in which the tubing was removed after 10 days the canaliculus again became obstructed; yet the dacryocystorhinostomy stoma remained open. It would seem, from this experience, that the polyethylene tubing should remain in the lacrimal canaliculus somewhere between 10 and 36 days to assure permanent reconstruction.

The plastic material polyethylene has fulfilled my original expectations with regard to minimal tissue reaction. In no case was there any significant irritation of the tissues by the polyethylene. In one case the tubing remained in the tissues for four months without inciting any visible foreign body response in the surrounding tissue. Spool cotton, which was used to suture the tubing into position in some cases, also seemed reasonably inert.

Polyethylene is a pliable material, and in cases in which the canaliculus is very narrow the passage of the tubing along the canaliculus is facilitated by the temporary insertion of a thread of silkworm gut through the lumen of the tubing. When the tubing is in position, the silkworm gut can be removed.

In my own experience polyethylene tubing has seemed the most satisfactory of the various materials previously described and utilized for the reconstruction of lacrimal canaliculi.

LACRIMATION IN NORMAL EYES

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THE FUNCTION of any healthy organ varies widely both at rest and when stimulated. Therefore any amount of tear flow which allows the eye to function normally and without discomfort must be considered as normal, at least for that particular eye. What are tears? Strictly speaking, tears are the fluid secreted by the lacrimal gland without the admixture of the secretion of the other glands of the conjunctiva. There is probably only one method to collect this secretion, namely, at the fistula of the lacrimal gland. This was done by Ahlström in one case, as cited by Schirmer.[1] He estimated the daily output of the lacrimal gland to be 4 gm. However, the fine tube pressed in the fistula itself must have acted as a stimulus to the lacrimal gland and caused increased secretion. Anyway, such a condition is very rare.

However, the watery fluid which accumulates in the conjunctival sac is generally considered as tears. This fluid is the product of the lacrimal gland, the accessory lacrimal gland, the Meibomian glands, and the mucous glands of the conjunctiva. The amount of this composite fluid will be the subject of discussion in this paper. The chemical composition of the normal tears is not discussed here, though there are indications (Meyer,[2] Klein,[3] Regan,[4] deRoetth,[5] Balik[6]) that qualitative changes are even more important in producing keratoconjunctivitis sicca than quantitative change.

When one is investigating the normal amount of tears, two problems arise. First, how large is the normal flow of tears when the eye is not subjected to irritation, and second, how large is the lacrimation when artificial stimulus is applied? Schirmer[1] determined the flow of tears in five subjects who had undergone extirpation of the lacrimal sac when all stimuli producing lacrimation were eliminated. These persons were placed in a room, and all stimuli to the eyes were avoided. He measured the time needed to form, and the weight of, the first drop, adding

1. Schirmer, O.: Studien zur Physiologie und Pathologie der Tränenabsonderung und Tränenabfuhr, von Graefes Arch. Ophth. **56**:197-291, 1903.

2. Meyer, K.: Mucopolysaccharides and Mucoids of Ocular Tissues and Their Enzymatic Hydrolysis, in Modern Trends in Ophthalmology, edited by Ridley, F., and Sorsby, A., New York, Paul B. Hoeber, Inc., 1940, Vol. 2, pp. 71-78.

3. Klein, M.: The Lacrimal Strip and the Precorneal Film in Cases of Sjögren's Syndrome, Brit. J. Ophth. **33**:387-388, 1949.

4. Regan, E.: The Lysozyme Content of Tears, Am. J. Ophth. **33**:600-605, 1950.

5. deRoetth, A.: The Dry Eye, Acta XVI Conc. Ophth., London **1**:456-464, 1950.

6. Balik, J.: The Lacrimal Fluid in Keratoconjunctivitis Sicca: A Quantitative and Qualitative Investigation, Am. J. Ophth. **35**:773-782, 1952.

to it the amount lost by evaporation from the exposed surface of the eyeball. This he calculated from an experiment in which he used a small vessel in the shape and size of the palpebral opening, filled with water. The amount evaporated from it in 16 hours was measured. From these data he estimated that with the least possible and only physiological stimulus, one eye produced 0.5 to 0.75 gm. of tears in 16 waking hours. He also proved that normal eyes do not secrete tears in sleep. The lacrimal gland, except during weeping, does not secrete without external stimuli. But just keeping the eyes open, even at room temperature, acts as a stimulus. However, only in special cases, that is, when the conjunctiva is normal and there is no drainage of tears through the nasolacrimal duct, can the determination of the flow of tears be carried out as Schirmer did.

For clinical purposes, Schirmer resorted to methods in which he measured the response of the tear-producing glands to a standard stimulus with a strip of blotting paper hooked over the margin of the lower lid. This response of the tear-producing glands to an artificial, nonphysiological stimulus should be called lacrimation. In his first method the stimulus was the strip itself resting on the conjunctiva. His second test consisted in irritating the nasal mucosa with a hair brush after the eye was anesthetized. The third method was similar to the second, but instead of his irritating the nasal mucosa, Schirmer had the patient look at the sun. He stated that on the average in normal cases the 30-mm. strip is moistened in five minutes with the first method. He said further, "In normal subjects I found the absolute low value [with the first method] to be 3 mm. in five minutes; yet such low values only rarely occur." A secretion of more than 15 mm. with the first method he considered normal but thought that patients having a moistening of the strip of less than 15 mm. should be examined with the second method, because damage to the excitolacrimal fibers or to the lacrimal gland is to be suspected. He also stated that if the strip is moist within 20 seconds with the first method hypersecretion is present. Beetham,[7] using Schirmer's first method on many normal eyes, found on several occasions a value as low as 10 mm. "A distance of less than 10 mm. in 5 minutes would signify, therefore, diminished lacrimal secretion." There is general agreement that Schirmer's methods are rather crude, yet at present the only practical ones for clinical determination of the lacrimation. The second method of Schirmer is a disagreeable procedure and has more pitfalls than the first. It is easier to see the condition of the conjunctiva and cornea than that of the inner part of the nose. A deviated septum, a large turbinate, mucous membrane covered with secretion or the height to which, or the angle at which, the hair brush is introduced in the nose can interfere with the result. Therefore, only the first method gained wide acceptance.

In order that values may be comparable, any method must be standardized. In 1941 I [8] recommended the use of Whatman No. 41 filter paper, but otherwise adhered strictly to Schirmer's technique. Schirmer said that at one end of the 35 by 5 mm. strip a length of 5 mm. is bent, the corners of this piece are cut off, and, with the aid of the bent piece the strip is hooked over the margin of the outer half of the lower lid and allowed to remain there five minutes. To be more specific, I

7. Beetham, W. P.: Filamentary Keratitis, Tr. Am. Ophth. Soc. **33**:413-435, 1935.

8. de Roetth, A.: On the Hypofunction of the Lacrimal Gland, Am. J. Ophth. **24**:20-25, 1941.

place it at the junction of the outer and the middle third of the lower lid. With this, Schirmer's standardized first method, I examined 162 eyes with no inflammatory disease. The values were read after five minutes, or the time within this period was noted at which the 30-mm. strip became moist in its entire length. It was found that lacrimation decreases with age and that about one-third of the persons above 40 years of age have a lacrimal production that Schirmer regarded as suspicious of damage to the excitolacrimal fibers.

In 1950 a new set of normal values for 300 patients over 50 years of age were presented.[5] One eye of each subject was tested. The values were read after five minutes, or the length of time was measured in which the entire length of the strip became moist. The strip which could have been moist in five minutes was estimated arbitrarily in arithmetical ratio; that is, when 30 mm. was moist in 2½ minutes, it was calculated that in 5 minutes 60 mm. would have been moist. The results are shown in Table 1. In all tables the results are given in millimeters of the strip of the test paper.

TABLE 1.—*Average Schirmer Values for Persons Older Than Fifty*

Age, Yr.	50-59	60-69	70-79	80 and Older
Values, Mm.				
Men	32	28.3	16.6	10
Women	37.3	27	18.2	15

TABLE 2.—*Average Secretion of Tears of Persons of Various Age Groups*

Age, Yr.	16-25	26-35	36-45	46-55	56 or More
Results, Mm.					
Males	18.0	19.1	16.8	12.6	11.5
Females	22.1	15.3	17.0	14.3	14.6

Henderson and Prough,[9] using Schirmer's first method, reported on the secretion of tears in 231 patients, or 462 eyes. There results are shown in Table 2.

Table 2 shows considerably lower figures than Table 1, though most of the persons examined belonged to a younger age group.

These authors did not measure the secretion of tears if it surpassed 25 mm. in five minutes and did not make allowance for such cases. They called attention to this fact by stating, "The length of the testing agent (25 mm.) necessarily prevents some subjects from exhibiting a greater flow of tears." They used "blotting paper" and applied the strip near the punctum, not in the temporal half of the lower lid. Another difference between my method and that of Henderson and Prough, though one which has no bearing on the figures, is that these authors tested the two eyes simultaneously, and I tested only one, almost always the left eye. However, though the numbers differ, their conclusions are similar to mine, namely, that, "age seems to be an influencing factor on secretion of tears." Further, "These values are so different in the same age group that it is difficult to propose

9. Henderson, J. W., and Prough, W. A.: Influence of Age and Sex on Flow of Tears, Arch. Ophth. **43**:224-231, 1950.

an exact limit of the normal." The authors found that young women (16 through 26) exhibited a definitely greater, and old women (beyond 60) a smaller, flow of tears than men of the same age groups, although the difference was slight. One of their important observations is that the majority of persons tested showed a difference of 3 mm. or less in the flow of tears from their two eyes.

Both Henderson and Prough's and my results are arbitrary. In my series the high values were determined by extrapolation in arithmetical ratio, and in theirs the lacrimation was measured only to 25 mm.

In a new series, I measured the entire lacrimation in five minutes. Only one eye, usually the left, of 827 persons was examined. Eyes with inflammatory conditions, glaucoma, or abnormality of the lid or lacrimal apparatus; eyes treated for a longer time with drops, or eyes which had undergone any kind of ophthalmic surgery were excluded, as well as the eyes of patients who had complaints referable to hyposecretion or hypersecretion of the lacrimal glands. Instead of the 35 mm. strip of Schirmer, I used a 65 mm. strip—the 5 mm. being for the conjunctival surface, and disregarded in measuring the result, just as Schirmer did. In case 60 mm. became moist within five minutes, a new strip, sometimes a third, or even a fourth, had to be used. A strip longer than 60 mm. cannot be used, because

TABLE 3.—*Lacrimation Measured with Modified Schirmer Test in Various Age Groups*

Age	6-9	10-19	20-29	30-39	40-49	50-59	60-69	70-79	80-
Males, mm.	63	59	40.8	41.2	31.1	22.8	21.4	16.2	11.5
No. of eyes tested	12	70	44	33	42	34	44	32	15
Females, mm.	63.8	63.4	47.4	34.2	38.3	26.4	23.9	17.4	16
No. of eyes tested	19	60	39	47	80	79	82	72	22

when moist it gets too heavy, easily falls out, or sticks to the cheek. Even this method does not give a true picture of the amount secreted, because the portion of the strip nearer the eye will be more soaked than the more distal end. Further, when the tears are rapidly formed, some may not be absorbed by the strip, but may roll off or may be drained by the nasolacrimal duct. Therefore, the high values, from about 60 mm. and more, should really be higher; more tears are produced than the Schirmer test would indicate. The average values according to sex and age groups are shown in Table 3.

Already Schirmer had stated that young persons produce more tears than older persons. This was found in my former investigations, but the decrease with advancing age is more precipitous than is shown in Henderson and Prough's table (Table 2). By the age of 40 the average values fall roughly to one-half those in the first decade of life. From then on there is a slower decrease, until the values in the ninth decade are one-fourth to one-fifth those in the first decade.

In all age groups except in that of the fourth decade, females had a slightly higher lacrimation, but difference between the sexes were not excessive. It is interesting, also, that in Henderson and Prough's experience women of the age bracket of 26 to 35 years had a lower flow of tears than did men of the same age—15.3, as against 19.1 mm.

Differences in the same age groups are extreme, this wide range being the reason for the difficulty in speaking of normal values. In all brackets except that

of young boys the extreme low was less than 10 mm. and the extreme high falls below 100 mm. only in the seventh decade. The extreme values for each group are shown in Table 4.

SUMMARY

Attention is called to the difference between "normal" flow of tears and "artificial" lacrimation. The former was determined by Schirmer in a few cases. The latter is of clinical interest. In a new series, 827 persons with normal eyes were examined with a modified Schirmer method, and in all cases the whole lacrimation in five minutes was measured. It was confirmed that the lacrimation decreases with age, the fall being precipitous between the ages of 20 and 50 years. In the ninth decade it is one-fourth to one-fifth that in the first two decades. In all age groups except the fourth females produce more tears. Differences in persons in the same age bracket are extreme. Therefore one must conclude that any amount of lacrimation is normal for that particular eye if it is functioning without discomfort.

TABLE 4.—*Extreme Values of Modified Schirmer Test in the Various Age Groups*

Age	6-9	10-19	20-29	30-39	40-49	50-59	60-69	70-79	80-
Males, mm.	16-152	4-225	6-180	2-183	3-169	4-90	6-90	4-42	1-30
Females, mm.	6-166	8-200	1-150	3-124	1-170	0-174	4-62	0-59	3-30

ELECTRORETINOGRAPHY IN CIRCULATORY DISTURBANCES OF THE RETINA

I. Electroretinogram in Cases of Occlusion of Central Retinal Vein or of One of Its Branches

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KARPE [1] concluded, from a study of five cases of thrombosis of the central retinal vein, that a favorable result may be anticipated when a normal or a supernormal electroretinogram is found, whereas the end-result may be unfavorable in cases when the electroretinogram is subnormal or negative.

From my own material [2] I confirmed this conclusion, emphasizing that there need be no parallel between the development of the electroretinogram and the altered appearance of the fundus. With the greater number of cases available, it is now possible to discuss this opinion in more detail.

METHODS AND MATERIAL

Technique.—The recording technique was the same as that described by Karpe. A modified contact lens was used, which may be regarded as a combined contact lens and blepharostat.[3] Experience with the use of this lens, which is provided with wings, has been excellent in a large number of cases.

The Electroretinogram.—When a light stimulus of short duration (1/25 second) is used, the electroretinogram is composed only of the components P III and P II (Granit), forming the a-wave and b-waves, respectively, of the electroretinogram. The b-wave develops to the full in dark adaptation of the retina and is closely related to the rods. To a certain degree, the a-wave is a function of the cones; however, the relationship has not yet been sufficiently clarified. Both components play an important role in the interpretation of circulatory disturbances of the retina.

Granit,[4] being a physiologist, ignored the clinical importance when, experimenting with the cat, he indicated only occlusion of the carotid arteries as a method of selectively removing component P II from the electroretinogram. In this experiment, in my opinion classic, he observed an accentuation of the a-wave and a diminution and final disappearance of the b-wave, dependent on the duration of the block. In some cases there was the initial development of a supernormal b-wave, but this was only temporary.

There is a striking agreement between Granit's findings and the various types of electroretinograms which can be recorded under clinical circumstances. Karpe,[1] in his monograph, indicated the clinical parallels.

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1. Karpe, G.: The Basis of Clinical Electroretinography, Acta ophth., Supp. 24, p. 1, 1945.

2. Henkes, H. E.: Use of Electroretinography in Disturbances of the Retinal and Choroidal Circulation, Proc. 16th Internat. Congress Ophth., London **2**:596-604, 1950.

3. Henkes, H. E.: Use of Electroretinography in Measuring the Effect of Vasodilation, Angiology **2**:125, 1951.

4. Granit, R.: Components of the Retinal Action Potential in Mammals and Their Relations to the Discharge in the Optic Nerve, J. Physiol. **77**:207, 1933.

Figure 1 shows the various kinds of electroretinograms which may be recorded in cases of occlusion of the central retinal vein or of one of its branches. They are recorded here with calibrations of 0.50 mv, the onset and cessation of the light flash are also recorded, with the aid of a second galvanometer.

I have divided electroretinograms of the negative type into a negative + and a negative — form. The latter corresponds to Karpe's negative electroretinogram. In this form the component P III predominates, as a result of which a normal P II assumes subnormal values. In my experience, however, another type also occurs, particularly in disturbances of the retinal circulation, in which the P II itself is also considerably increased, producing a supernormal b-wave. Both components are then enlarged. I have called this type negative +, recognizable by a pronounced a-wave and a supernormal, or at least normal, b-wave.

A value of 0.30 mv was selected at random as the threshold of the b-potential; because in the age group to which the patients mostly belonged (50 years and older), a value of 0.30 mv was found to be normal for the b-potential (Karpe [5]). Before the differentiation into negative + and negative — electroretinograms was made, the negative + electroretinograms were placed in the group of normal or supernormal electroretinograms. Before judging the retinal circulation, however, it is desirable to ascertain the value and the course of both the a- and the b-waves.

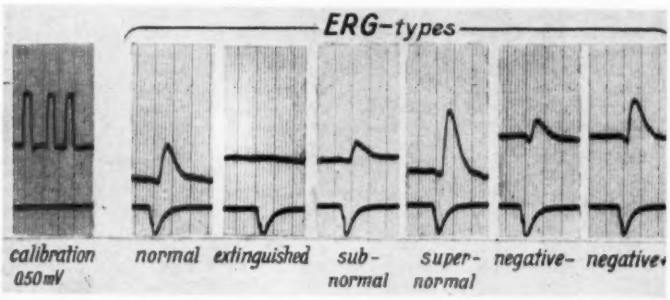

Fig. 1.—Various types of electroretinograms, preceded by a calibration of 0.50 mv. Below is the recording, with the aid of a photometer, of a light flash of 20 lux for 1/25 second. Time basis: distance between thick lines, 0.1 second; distance between thin lines, 0.02 second.

The other electroretinographic types—supernormal, normal, subnormal, and extinguished—bear relation only to the amplitude of the b-wave; in these forms the a-wave may be present, but it is not accentuated.

Material.—Records are presented of 61 patients (35 men and 26 women) who were treated for occlusion of the central retinal vein or of one or more of its branches; after one year one of the patients had a recurrence in the other eye; so the material comprises 62 eyes.

In the Table the cases are divided into three groups: those with total occlusion of the central retinal vein, those with partial occlusion of the central retinal vein, and those of occlusion of one or more branches of the central retinal vein. The time elapsed after onset of the symptoms is recorded.

In Group 2, that of the partial occlusion of the trunk, 15 cases are listed. In these cases the picture of occlusion of the central vein was observed ophthalmoscopically, with, however, preservation of fairly good macular function in the eye, a classification which is common in this clinic.

In Group 3 (22 cases) one is struck with the markedly higher incidence of occlusion of the superior temporal vein. This is familiar from the literature. Ennema,[6] in this connection, indicated that in the fundus in hypertension the arteriovenous crossings are predominant in the temporal retina.

5. Karpe, G.; Rickenbach, K., and Thomasson, S.: Clinical Electroretinogram: I. Normal Electroretinogram Above 50 Years of Age, Acta ophth. **28**:301, 1950.

6. Ennema, N. C.: Over venesluiting in het netvlies, Thesis, Amsterdam, Netherlands, 1940.

					Affected Eye			Sound Eye			
						ERG			ERG		
Case No.	Sex	Age	Onset of Symptoms		Vision at First Examination	Type	b-Potential, mv.	Vision at First Examination	Type	b-Potential, mv.	Ophthalmoscopic Picture
					1. Thrombosis of Central Vein						
1	F	68	1 day	OD	1/60	Neg.+	0.37	8/10	Neg.+	0.44	Hypertension +; diabetic changes
2	M	66	2 days	OS	1/60	Neg.—	0.12	1/∞	Neg.+	0.44	Syphilitic atrophy of optic nerve
3	F	69	2 days	OD	5/60	Neg.—	0.23	10/10	Neg.+	0.47	Hypertension
4	M	64	3 days	OD	1/10	Subnorm.	0.13	10/10	Norm.	0.30	Hypertension
5	M	57	4 days	OD	5/60	Neg.—	0.27	10/10	Neg.—	0.22	Normal
6	M	62	7 days	OS	1/10	Neg.—	0.11	7/10	Subnorm.	0.15	Degeneration of macula
7	M	59	10 days	OD	1/10	Neg.—	0.25	10/10	Norm.	0.38	Hemorrhage on disk
8	M	62	10 days	OD	1/60	Neg.—	0.27	10/10	Neg.+	0.33	Normal
9	M	61	14 days	OS	5/60	Neg.+	0.37	10/10	Neg.+	0.46	Normal
10	F	63	14 days	OS	4/60	Neg.+	0.56	10/10	Supernorm.	0.48	Normal
11	M	66	14 days	OD	2/10	Neg.—	0.08	10/10	Subnorm.	0.23	Hypertension
12	M	67	3 wk.	OD	1/60	Neg.—	0.05	7/10	Norm.	0.34	Normal
13	M	64	3 wk.	OS	1/2/60	Subnorm.	0.12	8/10	Subnorm.	0.16	Hypertension
14	M	67	3 wk.	OD	1/10	Norm.	0.31	8/10	Neg.+	0.50	Hypertension
15	M	68	4 wk.	OD	1/2/60	Neg.—	0.11	9/10	Norm.	0.33	Normal
16	M	65	5 wk.	OD	2/60	Subnorm.	0.14	10/10	Norm.	0.33	Narrow retinal vessels
17	F	76	6 wk.	OS	4/10	Norm.	0.29	6/10	Norm.	0.32	Hypertension
18	F	62	2½ mo.	OD	2/300	Subnorm.	0.20	10/10	Subnorm.	0.19	Normal
19	M	70	Months	OS	1/60	Neg.—	0.20	7/10	Norm.	0.34	Normal
20	M	67	Months	OS	1/10	Subnorm.	0.17	9/10	Norm.	0.29	Normal
21	M	67	3 yr.	OD	1/300	Subnorm.	0.17	6/10	Norm.	0.32	Normal
22	F	47	Years	OD	1/∞	Neg.—	0.29	8/10	Norm.	0.31	Normal
23	M	77	Years	OS	1/60	Subnorm.	0.21	9/10	Norm.	0.31	Normal
24	M	64	Unknown	OD	1/∞	Exting.	0	2/10f	Subnorm.	0.20	Glaucomatous cupping of disk
25	M	60	Unknown	OS	1/∞	Subnorm.	0.20	....	Eye enucleated, owing to hemorrhagic glaucoma		
					2. Partial Thrombosis of Central Vein						
26	M	42	3 days	OS	4/10	Norm.	0.28	7/10	Subnorm.	0.23	Myopia gravior
27	F	45	6 days	OS	1/60	Neg.+	0.63	6/10	Neg.+	0.50	Normal
28	M	53	7 days	OS	7/10	Neg.+	0.54	5/10	Neg.—	0.23	Strabismus
29	M	58	7 days	OD	1/10	Neg.+	0.30	10/10	Neg.+	0.47	Hypertension
30	F	65	1 wk.	OS	4/10	Norm.	0.37	10/10	Norm.	0.34	Normal
31	F	55	10 days	OD	5/10	Neg.+	0.44	1/10	Norm.	0.43	Atrophy of optic nerve
32	M	76	10 days	OS	7/10	Norm.	0.33	7/10	Norm.	0.37	Normal
33	M	77	4 wk.	OD	5/10	Supernorm.	0.47	6/10	Supernorm.	0.60	Glaucomatous cupping of disk
34	M	52	4 wk.	OS	9/10	Neg.+	0.34	10/10	Neg.—	0.22	Normal
35	F	63	4 wk.	OD	8/10	Neg.—	0.23	10/10	Neg.+	0.38	Hypertension
36	M	55	6 wk.	OD	8/10	Neg.—	0.25	10/10	Neg.—	0.22	Normal
37	F	71	2 mo.	OS	8/10	Neg.+	0.42	1/60	Norm.	0.34	Degeneration of macula
38	F	67	Months	OS	8/10	Neg.+	0.31	2/60	Neg.—	0.26	Local sclerosis of retinal vessels
39	M	61	Months	OD	6/10	Subnorm.	0.16	7/10	Norm.	0.37	Normal
40	M	66	Unknown	OD	10/10	Neg.—	0.23	10/10	Subnorm.	0.24	Hypertension
					3. Thrombosis of Retinal Vein						
41	M	69	2 days	OS	5/10	Neg.+	0.40	2/10	Neg.—	0.24	Old thrombotic changes
42	F	67	2 days	OS	5/60	Neg.+	0.38	10/10	Neg.+	0.37	Hypertension
43	F	53	3 days	OD	8/10	Norm.	0.41	8/10	Norm.	0.43	Hypertension
44	F	39	5 days	OS	5/10	Neg.—	0.29	10/10	Neg.—	0.27	Hypertension
45	M	61	7 days	OD	8/10	Neg.+	0.37	10/10	Neg.+	0.37	Normal
46	M	68	12 days	OD	1/60	Subnorm.	0.15	10/10	Supernorm.	0.48	Normal
47	F	64	2 wk.	OD	1/300	Neg.—	0.29	10/10	Supernorm.	0.46	Hypertension
48	F	65	3 wk.	OS	2/10	Norm.	0.30	10/10	Norm.	0.28	Normal
49	M	71	3 wk.	OS	5/10	Norm.	0.29	9/10	Norm.	0.30	Normal
50	F	61	3 wk.	OS	5/10	Subnorm.	0.24	10/10	Subnorm.	0.22	Normal
51	F	74	3 wk.	OS	2/60	Neg.—	0.28	1/10	Neg.—	0.27	Hypertension
52	F	60	4 wk.	OD	2/60	Neg.+	0.50	6/10	Neg.+	0.51	Normal
53	F	75	4 wk.	OS	2/10	Subnorm.	0.18	9/10	Subnorm.	0.21	Normal
54	M	51	6 wk.	OS	9/10	Neg.+	0.38	10/10	Norm.	0.37	Hypertension
55	M	63	Weeks	OD	1/60	Neg.—	0.14	10/10	Neg.+	0.45	Normal
56	F	65	2 mo.	OS	3/10	Supernorm.	0.57	9/10	Norm.	0.33	Hypertension
57	M	67	3 mo.	OS	5/10	Neg.—	0.27	10/10	Subnorm.	0.23	Sclerosis of retinal vessels
58	F	52	Months	OD	1/300	Neg.+	0.38	10/10	Neg.+	0.44	Hypertension
59	F	71	Unknown	OD	6/6	Neg.+	0.43	6/6	Neg.+	0.52	Normal
60	F	55	Unknown	OD	5/10	Neg.+	0.36	10/10	Neg.+	0.36	Hypertension
61	F	60	Unknown	OD	4/10	Neg.—	0.23	10/10	Norm.	0.36	Normal
62	M	58	Unknown	OD	1/10	Neg.+	0.33	9/10	Norm.	0.39	Normal

In Figure 2 fifty cases are plotted according to the age group, this incidence being in accordance with the distribution in the extensive material of Brændstrup [7] and others. From this graph, it is evident that venous occlusion occurs more frequently in men than in women and that the incidence increases considerably in persons above the age of 60.

Thirty patients could be regularly examined electroretinographically; 10 patients were followed for over one year, and 12, for at least six months; for 9 the electroretinogram could be taken regularly only for a shorter period. On 30 patients only occasional observations could be made.

RESULTS

The table shows that a normal fundus and a normal electroretinogram were found in the sound eye in only a comparatively small portion of the material exam-

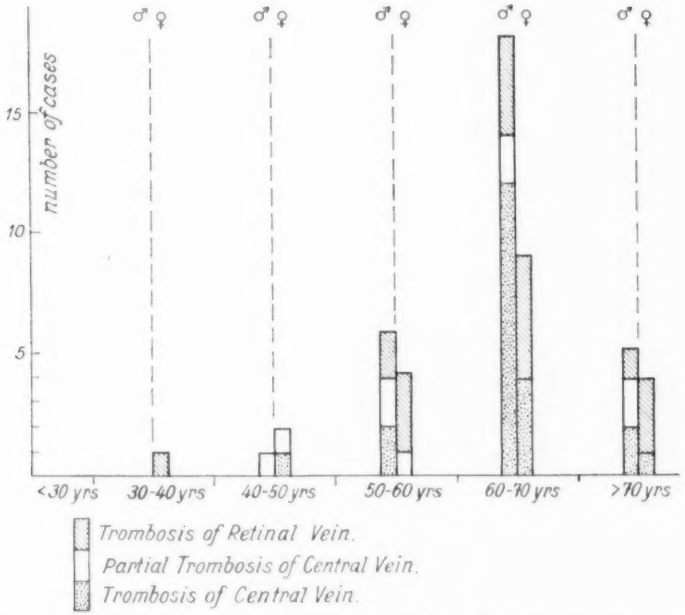

Fig. 2.—Various types of occlusion of the central retinal vein or its branches, plotted according to age.

ined. The electroretinogram only was normal in 23 cases (37%), whereas the fundus showed no abnormality in 29 cases (48%).

Brændstrup [7] recorded that no abnormalities were found in 45% of the eyes, while on repeated examination only 36% of the so-called sound eyes were without ophthalmoscopic abnormalities. The concept of electroretinography as an objective method of examination fits in well with this observation. It is not possible actually to assign a special electrotretinogram to each of the three groups of venous obstruction. In group 1, at the first examination electroretinograms in cases of occlusion

7. Brændstrup, P.: Central Retinal Vein Thrombosis and Haemorrhagic Glaucoma, Acta ophth., Supp. 35, p. 1, 1950.

of the venous trunk were clearly dominated by the subnormal b-wave, usually combined with a pronounced a-wave. The negative — electroretinogram is the type of most frequent occurrence in this group (20 cases of subnormal b-waves, as compared with 5 cases of normal or supernormal b-waves).

In group 2, that of the partial occlusion of the central vein, the situation is reversed. Here, the normal and supernormal b-waves predominate, and they may or may not be combined with a pronounced a-wave (11 cases of a normal or supernormal b-wave, as compared with 4 cases of a subnormal b-wave). The electroretinogram occurring most frequently is the negative + type.

In group 3, that of the branch occlusions, the supernormal and normal b-waves are somewhat more frequent than the subnormal b-waves, but it seems hardly justifiable to associate a special type of electroretinogram with the branch occlusions

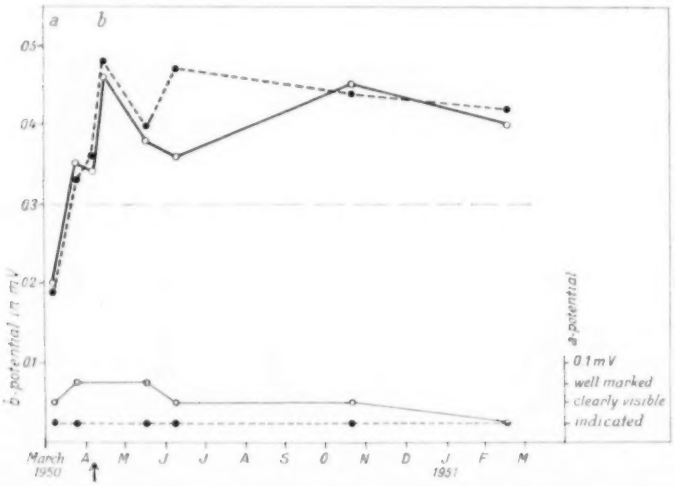

Fig. 3 (Case 18).—Curves showing the development of the a-potentials (below) and b-potentials (above) of the electroretinogram of a patient with occlusion of the central vein. With the treatment instituted and rest in bed, striking improvement in the electroretinogram was maintained, even after the patient's discharge from the clinic (arrow). Values for the right eye are indicated by the line of circles; values for the so-called normal (left) eye, by the line of solid circles and dashes.

(13 cases of normal and supernormal b-waves, as compared with 9 cases of subnormal b-waves).

The curves now to be discussed show the course of the a- and b-waves during treatment of several patients who could be regularly examined electroretinographically.

Case 18 (Table, Group 1).—The patient had had poor vision in the right eye for 2½ months. The clinical diagnosis was thrombosis of the central retinal vein of the right eye. On her admission to the hospital, the electroretinograms were subnormal in the affected, as well as in the normal, eye, the latter showing no abnormalities ophthalmoscopically. The low b-potential of the so-called normal eye seemed to justify the conclusion that the circulation was not at all normal.

Under the influence of rest in bed and the treatment given, saltless diet and use of digitalis, anticoagulants, vasodilators, rutin, and ascorbic acid, the b-potential improved notably in the affected, as well as in the normal, eye (Fig. 3).

Visual improvement, from 2/300 to 4/10, more or less paralleled the return to normal of the a- and b-potentials, which originally had reached supernormal values. After her discharge, the b-potential remained at about the same level; in spite of the resumption of normal daily duties. After a few months, as is frequently observed, the macula showed degeneration.

Maintenance of the normalized a- and b-waves is, in my opinion, the best guarantee of the continuation of a reasonable retinal circulation.

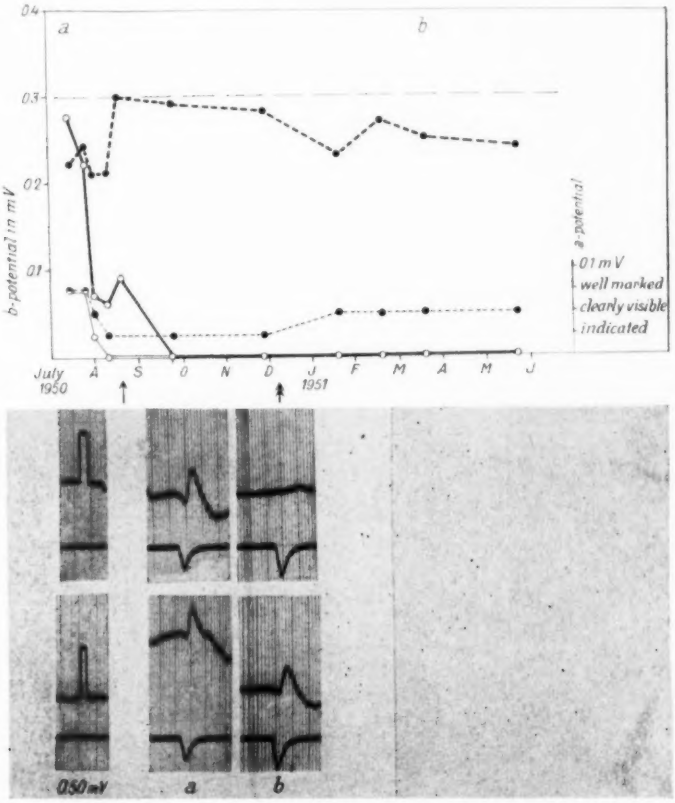

Fig. 4 (Case 5).—Curves showing the development of a- and b- potentials in the electroretinograms of a patient with occlusion of the central retinal vein of the right eye. After discharge (arrow) there was further lowering of the b-potential in the affected right eye (line of hollow circles). The double arrow marks the occurrence of hemorrhagic glaucoma. The b-potential of the left eye remained at the same level (line of solid circles and dashes). The electroretinograms of July, 1950, and March, 1951, are placed under the graph, together with a calibration of 0.50 mv. Electroretinograms for the right eye are shown above the electroretinograms of the left eye.

CASE 5 (Table, Group 1).—The patient complained of decreasing vision in the right eye for the last few days. The clinical diagnosis was thrombosis of the central retinal vein of the right eye.

From Figure 4 it can be seen that, although the b-potentials were at first fairly well developed in both eyes, while the a-wave was pronounced in both eyes, the circulation in the affected (right) eye passed through a critical phase. In spite of rest in bed and the treatment given, i. e., administration of anticoagulants, rutin, and ascorbic acid, the b-potential in the affected eye decreased.

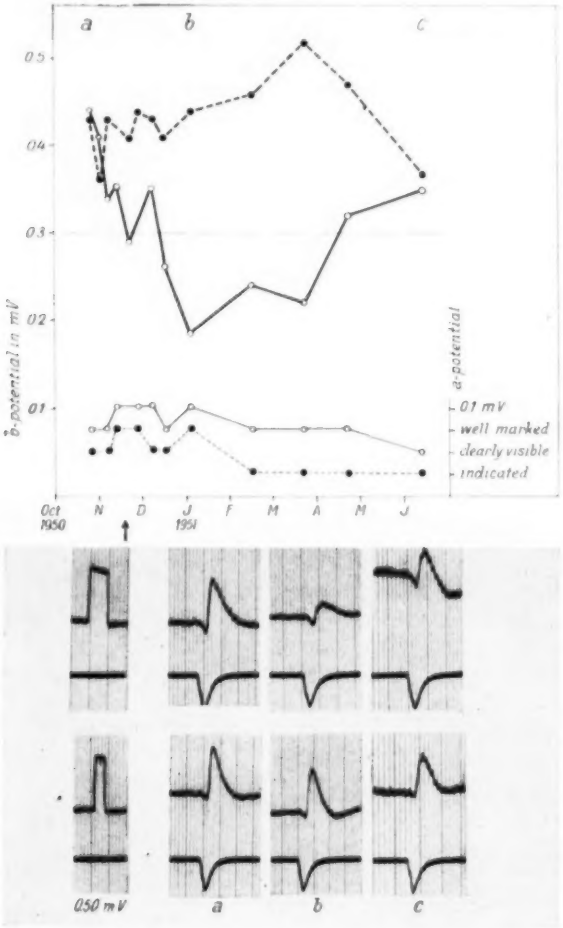

Fig. 5 (Case 31).—Curves showing the values for the a- and b-potentials, together with a few samples of electroretinograms recorded at times, *a*, *b*, and *c*. An initial drop in the b-potential in the affected eye (partial occlusion of the central retinal vein of the right eye) was halted one month after discharge (arrow), after which there was a return to normal in the a-potentials, as well as in the b-potentials, of both eyes. Values for the right eye are indicated by the line of hollow circles; values for the left eye, by the line of solid circles and dashes.

Vision did not change in correspondence with this change in potential; in fact, vision improved during this period from 5/60 to 3/10, on discharge, as a result of the resorption of some of the hemorrhages in the macular area.

After the patient had been discharged from the hospital, the b-potential fell to 0 mv, the latter being associated with a lowering of the vision to 1/—$_{50}$. An unfavorable outcome for the b-potential was feared; indeed, in December, 1950, hemorrhagic glaucoma developed (double arrow), with total loss of function in the eye.

The normal eye, without abnormalities of the fundus, stayed in good condition, although in my opinion the pronounced a-wave indicates a slight, but reparable, circulatory disturbance.

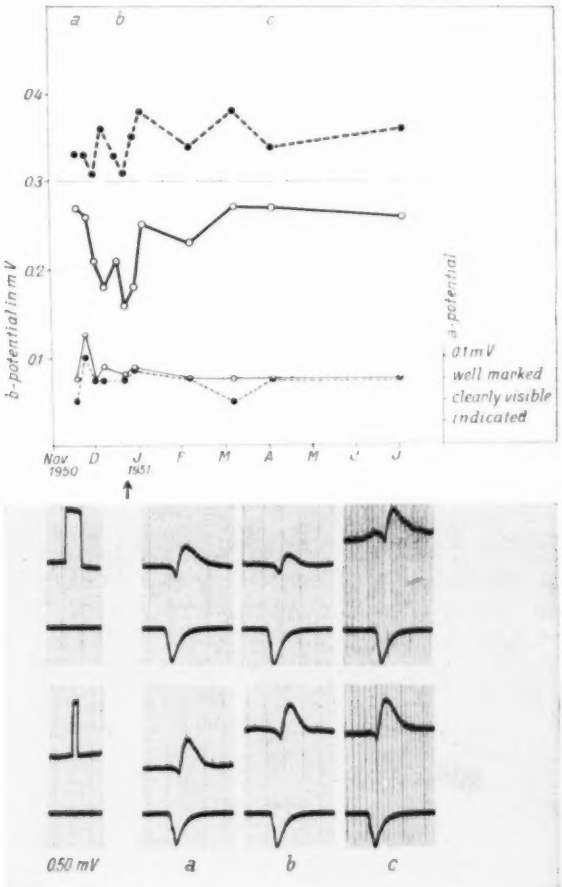

Fig. 6 (Case 8).—Curves showing the course of the a- and b-potentials plotted against the time, in months, in a case of fresh occlusion of the central retinal vein of the right eye (line of hollow circles). The b-potential, after an initial drop, did not return to normal until after the patient's discharge from the hospital, in spite of the treatment given. The pronounced a-potentials remained more or less stationary, as the result of the existing hypertension. Examples of electroretinograms of the affected (right) eye are shown above those of the sound (left) eye, taken at times *a*, *b*, and *c*.

CASE 31 (Table, Group 2).—In Figure 5 the a- and b-potentials are plotted from the electroretinograms of a patient with partial occlusion of the central retinal vein and of the right eye.

The falling b-potential in the affected eye apparently could not be influenced by treatment. The decrease progressed even after the patient's discharge from the hospital (arrow). An unfavor-

able outcome was feared. Fortunately, a reversal of the process occurred after a few months, though this was not apparent from the vision, which, in spite of a normalization of the a- and b-potentials that eventually developed, went back to 5/30. The prognosis with respect to the retinal circulation can be said to be favorable.

Case 8 (Table, Group 1).—In figure 6 the course of the a- and b-potentials is shown in a case of fresh occlusion of the central retinal vein of the right eye. The patient had general hypertension, without however, the fundus of the unaffected eye being abnormal.

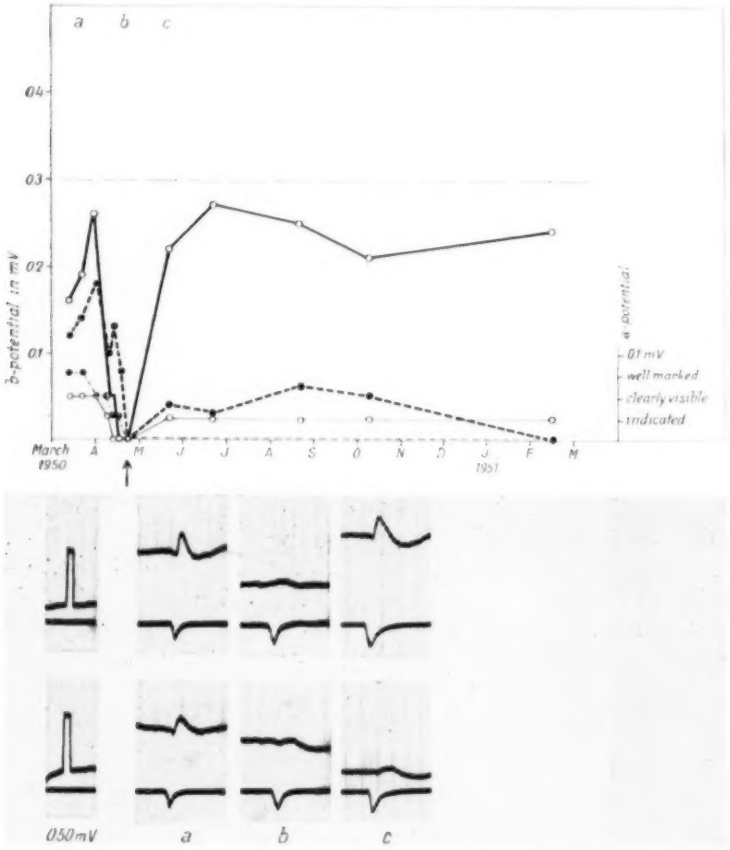

Fig. 7 (Case 13).—Curves for a- and b-potentials and electroretinograms, as described in previous figures, in a case of occlusion of the venous trunk of the left retina (line of dashes and solid circles). The fundus of the right eye was typical of hypertension. Marked changes occurred in the b-potentials, without producing any effect on the vision in the "non-thrombosed" eye. The electroretinograms of the right eye are reproduced above those of the left eye.

The electroretinogram of the affected eye showed an initial fall in its b-potential, which was not halted until his discharge from the hospital, in spite of the treatment given. The a-potentials showed little tendency to fall. The b-potential of the unaffected eye was maintained at a normal level.

Case 13 (Table, Group 1).—The fundus of the right eye presented an obvious picture of hypertension. An occlusion of the central retinal vein of the left eye had been present for

three weeks. In Figure 7 the curves of the a- and b-potentials of the electroretinogram are represented for the two eyes. The noteworthy fact is demonstrated that the acute decreases in the b-potentials during, and in spite of, the clinical treatment (rest in bed, saltless diet, and use of anticoagulants and vasodilators) were not accompanied by any change in the appearance of the fundus. On the date of the patient's discharge (against advice) there was hardly any sign of a b-potential on either side (Moment *b*). In the eye which showed no sign of an occlusion the b-potential returned to almost normal values, without there being any effect on the vision.

Vision in the right eye stayed at about 7/10 all the time that the electroretinograms were being recorded. Vision in the left eye dropped from 1/60 to 1/300. The b-potential remained low in the affected (left) eye, even after it had regained recordable values.

COMMENT

It is recognized that the vision of patients who have total occlusion of the central retinal vein is considerably more disturbed than the vision of patients who have partial occlusion of the central vein or occlusion of a branch of the central vein.

From the electroretinograms discussed, it appears that the macular function does not play a predominant role with respect to the prognosis of the retinal disease, for the vision does not bear any constant relation to the circulatory conditions which occur in the retina as a whole. The electroretinogram, on the contrary, does bear some relation. It is, in my opinion, the expression of the momentary condition of the entire circulatory apparatus of the retina.

In this connection, it is interesting that Brændstrup pointed out that the effect of any treatment can and should be judged only after a certain degree of recovery of the retinal circulation has been reached. This recovery, and, in general, any change in the state of the retinal circulation, cannot in my opinion be adequately judged objectively, either with the ophthalmoscope or on the basis of macular function. Only the electroretinogram gives any objective information in this respect.

A fall in the b-potential may be interpreted as indicating a deterioration in the metabolic condition of the retina. In these cases of occlusion of the central retinal vein or of one of its branches, it is obvious that the circulatory system is responsible. The development of an increase in disproportion between the circulating system, on the one hand, and a functional retinal element, on the other, must, in my opinon, be accepted as an explanation of the change in the electroretinographic potentials.

An improvement in, or a return to normal of, the a- and b-potentials indicates improvement in the state of the circulation. Such changes in the electroretinogram may or may not be reflected in the macular function.

One should, to my mind, speak of a partial occlusion of the central retinal vein only when the b-potential of the electroretinogram gives normal or supernormal values, preferably combined with a pronounced a-wave, by definition a negative + electroretinogram, even when the vision is poor. It is unsound to make a diagnosis of partial occlusion of the central vein on the basis of the fundus picture with the retention of relatively good vision. It is correct, on the other hand, to speak of a total occlusion in cases in which the electroretinogram shows a subnormal b-wave, preferably in combination with a pronounced a-wave, by definition a negative — electroretinogram, even when vision is reasonably good. It is doubtful whether this combination exist, at least when no cilioretinal vessels are present.

When the process has existed for a longer period, I have noticed, in various cases, that the electroretinogram returns to normal, after or as a result of treatment. One must assume that a collateral circulation develops, rather than that the lumen of the occluded vessel is restored. This normalization of the electroretinogram can proceed only so far, and if there are retinal elements present which recover from reparable damage. The irreparable changes that develop, nevertheless, will eventually produce such an effect that the ultimate height of the b-potential will be unfavorably influenced.

The cases described above demonstrate that the phenomena of retinal hypertension are expressed in the a-potentials, as well as in the b-potentials, of the electroretinogram. An increased a-potential is found repeatedly in retinal, as well as in general, hypertension. Improvement in the general hypertension is usually accompanied by a return to normal of the a-wave (Figs. 3 and 5). This corresponds with the abolition of the slight, but already long-standing, disturbance in the metabolic condition of the retina. Evidently, in these cases no irreparable change in the retina has occurred.

When an obvious retinal hypertension exists (Fig. 7), the metabolic state of the retina may be so severely disturbed that marked changes in the b-wave may develop. The electroretinogram may even completely disappear, temporarily. The function (visual acuity and visual field) may be preserved in spite of this disturbance, at least if the condition does not exist too long.

Neither the ophthalmoscopic picture nor the function of the eye, in the case described, gave the slightest information concerning these transient disturbances in the metabolism; only the electroretinogram could supply this information.

TREATMENT

It is clear, as is evident from the facts presented, that the treatment of this disease must be viewed with a high degree of skepticism.

In fresh cases, the treatment must be directed toward the improvement of (*a*) the general condition of the patient, and thus (*b*) the local circulatory disturbances in the retina.

The patient's general condition must be improved with general measures, i. e., rest in bed, saltless diet, use of sedatives, and, eventually, treatment of the insufficient general circulation. For direct intervention in the retinal process, one should consider the use of anticoagulants, to counteract and prevent further thrombus formation; vasodilators, to combat eventual occurrence of peripheral and local vasospasms and to promote the collateral circulation, and drugs, such as rutin and ascorbic acid, to strengthen the vessel walls.

The institution of treatment is also useful when the occlusion is of long standing. Anticoagulants can then no longer be considered. The value of the beneficial effect of treatment on the sound eye, as accessory to the favorable influence of the entire organism, essentially must be considered. This effect can be well recorded by means of the electroretinogram.

SUMMARY AND CONCLUSIONS

In 63 cases of occlusion of the central retinal vein or of one of its branches electroretinographic examinations were performed.

A curve which follows the course of the a- and b-potentials of the electroretinogram over a long period gives objective information on the state of the retinal circulation and is of value in the prognosis in cases of this disease.

A negative — electroretinogram must be considered typical of total occlusion of the central retinal vein. The negative + electroretinogram predominates in cases in which the occlusion is not complete. It is not possible to show any specific type of electroretinogram in cases of occlusion of a branch of the central vein.

The division of the cases of thrombosis of the central vein into those of total and those of partial occlusion should be made on the basis of the electroretinographic results; vision is of minor importance.

The development of hemorrhagic glaucoma could in one case be foreseen from the electroretinograms.

The treatment must first be directed toward improvement in the general condition of the patient; such treatment likewise benefits the sound eye. In a large number of cases electroretinographic abnormalities were discovered, necessitating the institution of general and dietetic measures.

THE GRAM-NEGATIVE DIPLOBACILLUS IN HYPOPYON KERATITIS

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HYPOPYON keratitis due to infection with the Gram-negative diplobacillus is an uncommon condition. Since the causative organism is of little general interest, bacteriologists have not studied it intensively. Ophthalmologists, on the other hand, find the organism very important but have given it little attention because of the special techniques required in its study. Petit,[1] in 1898, on the basis of his clinical and bacteriologic investigation of three cases, divided diplobacillary infections into two groups. Since then, ophthalmologists have considered central hypopyon keratitis to be due to the diplobacillus of Petit and marginal keratitis or conjunctivitis to be due to the Morax-Axenfeld bacillus (Moraxella lacunata). It is the purpose of this paper to demonstrate that this rather arbitrary division is not well founded on either clinical or bacteriologic grounds.

HISTORICAL REVIEW

In July, 1896, Morax [2] published the first paper on the Gram-negative diplobacillus. He described it as the causative agent of subacute conjunctivitis. The following month, Axenfeld presented his independent investigation at the International Ophthalmological Congress at Heidelberg, calling the condition chronic diplobacillary conjunctivitis. He published his detailed report the following year.[3] The organism soon became known as the Morax-Axenfeld bacillus. In 1900 Eyre [4] applied the name lacunatus to it because of its characteristic tendency to form lacunae, or pits, in Löffler's solid medium. However, Petit's paper had the greatest effect on the present concept of diplobacillary keratitis. He believed that his organism was different from that previously described by Morax and Axenfeld. His was associated with a central hypopyon ulcer (ulcus serpens corneae); theirs, with subacute conjunctivitis, and sometimes mild marginal corneal ulcers. His

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1. Petit, P.: Sur une forme particulière d'infection cornéene à type serpigneux, Ann. ocul. **140**:166, 1899.

2. Morax, V.: Note sur un diplobacille pathogène pour la conjonctivite, Ann. Inst. Pasteur **10**:337, 1896.

3. Axenfeld, T.: Über die chronische Diplobacillenconjunctivitis, Zentralbl. Bakt. **21**:1, 1897.

4. Duke-Elder, W. S.: Text-Book of Ophthalmology, Vol. 2, St. Louis, C. V. Mosby Company, 1938.

organism would proliferate at lower temperatures, grow on simpler media, and liquefy coagulated serum and gelatin more effectively.

Chaine [5] thought these organisms were two different forms, because he found no serologic relations between the two by agglutination, precipitation, or complement fixation tests. Other authors, such as Paul [6] and Tooke,[7] believed that they really were the same organism. Many cases of ulcerative keratitis have been reported as being due to the Morax-Axenfeld bacillus,[8] and therefore much confusion has arisen.

CLINICAL PICTURE

To appreciate the marked difference in the clinical picture of a central ulcer with hypopyon and that of marginal ulceration associated with conjunctivitis, one must recall the structural and functional differences between the central and the marginal portion of the cornea. The marginal portion is much more like conjunctiva than is the central area. It is thicker, has a heavier covering of epithelium, is better protected by the lids, and is in closer association with blood vessels. These vessels ensure it better nutrition, as well as a more concentrated supply of immune bodies, or toxins, if either is present.

It is generally believed that marginal ulcer is caused by a toxin, which, elaborated during conjunctivitis, seeps into the peripheral corneal tissue, where it sets up irritation, inflammation, necrosis, and then ulceration. Such an ulcer rarely yields organisms on culture. If it does one should suspect contamination from the neighboring conjunctiva. Central ulcer, on the other hand, is believed to be due to direct inoculation of the weaker, and less well-protected, central portion of the cornea. Thygeson [9] suggested that central ulcer always is preceded by trauma to the epithelium. The marginal ulcer is usually multiple, small, shallow, and quick to heal, once the conjunctivitis is cured. The central ulcer is large, deep, nearly always single, associated with hypopyon, and yields the causative organisms on scraping. Since the marginal ulcer is associated with indolent conjunctivitis, it is presumed that there is sufficient time for antibody formation, but central ulcer is so severe and fulminating that there is little time for antibody formation.

Constitutional factors also affect the clinical picture, central corneal ulceration being commoner in the aged, the debilitated, and the chronically alcoholic. In fact, every patient with central corneal ulcer seen at Bellevue Hospital in the past two years has been such a person. This factor also explains why cases of central corneal ulcer are commoner in municipal hospitals than in office practice.

The clinical picture depends upon local conditions in the eye and the general status of the patient, not necessarily on the type of infecting organism. A great variety of bacteria can cause primary hypopyon keratitis. Thygeson [9] reported 70%

5. Chaine, R.: Le diplobacille de Morax et le diplobacille liquéfiant de Petit (étude comparée), Ann. ocul. **152**:330, 1914.

6. Paul, L.: Über Hornhautulcerationen durch Diplobazillen, Klin. Monatsbl. Augenh. **46**:543, 1908.

7. Tooke, F. T.: Morax-Axenfeld Conjunctivitis, Ophth. Rec. **15**:194, 1906.

8. Axenfeld, T.: The Bacteriology of the Eye, Translated by Angus McNab, London, Ballière, Tindall & Cox, 1908.

9. Thygeson, P.: Acute Central (Hypopyon) Ulcers of Cornea, California Med. **69**:18, 1948.

of his cases of central ulcer to be due to Pneumococcus, and only 18% to Gram-negative bacilli. Of our latest 12 cases Pneumococcus was the infecting organism in 2 (16%) and Gram-negative bacilli in the remaining 84%. In two the ulcer was due to Pseudomonas aeruginosa; in one, to Aerobacter aerogenes; in one to Escherichia coli, and in six to the Morax-Axenfeld bacillus. This would seem to indicate an absence of bacterial specificity for primary central hypopyon ulcer.

In our cases of hypopyon keratitis due to Gram-negative rods, the patients characteristically complained of little or no pain. Usually the condition started with trauma to the eye and/or an infection of the upper respiratory tract. The central ulcer enlarged slowly as the eye turned red and the visual acuity decreased. The most characteristic sign was the deep, abscess-like development of the process. The ulcer progressed painlessly until there developed secondary glaucoma, and often a descemetocele. These features contrasted sharply with the severe pain, photophobia, and lacrimation typical of pneumococcic ulcers. These differences are compared briefly in the following tabulation, adapted from McNab.[10]

Diplobacillary	Pneumococcic
Often history of chronic or recurrent angular blepharoconjunctivitis	History of "watery eye," usually dacryocystitis, mucocele, or stricture of nasal duct
Trauma frequent	Trauma practically always present
Small, deep ulcer	Large, shallow ulcer
Border not well defined; edge less infiltrated than base	Border densely infiltrated, undermined, advancing in one direction
Descemetocele common in middle stage of process	Descemetocele rare
Iritis of mild type	Iritis varying in intensity
Hypopyon small, with flat upper border	Hypopyon usually large
Other gray infiltrates in cornea, usually marginal in position	Rarely other infiltration; when present, dense, white, round, and rapidly breaking down
Infiltration ring around ulcer sometimes; characteristically, infiltration in superficial and deep layers, with a transparent layer between them	No infiltration ring, but a densely infiltrated advancing margin
Pain slight, sometimes absent	Pain usually intense, severe enough to cause insomnia
Progress usually slow; rarely more than 3-4 mm. in extent after one week's duration	Progress rapid; whole cornea may be destroyed in a few days
Diplobacilli found in base of ulcer	Pneumococci found in advancing margin of ulcer

Soudakoff,[11] in describing cases ascribed to the diplobacillus of Petit, said that the disease usually runs a mild course. Elliot and associates,[12] reporting cases of similar etiology, stressed the severity of the lesions and the poor prognosis. We are inclined to agree with the latter, as the ocular destruction we have seen is impressive.

INCIDENCE

Axenfeld considered diplobacillary infections among the commonest and most widespread of all ocular diseases. Epidemics have occurred, but they have not been severe. In general, the condition is endemic. We obtained some of our material for study from a hospital where it is endemic. Persons of every age and race may be affected. Adults are attacked most commonly, especially the aged and debilitated; however, cases have been reported in the newborn. In Negroes it has been reported

10. McNab, A.: Ulceration of the Cornea, London, Ballière, Tindall & Cox, 1907.

11. Soudakoff, P. S.: Keratitis Ulcerosa and Nonulcerosa Produced by the Diplobacillus of Petit: Report of 3 Cases, Chinese M. J. **50**:1415, 1936.

12. Elliot, A. J.; Chamberlain, W. P., Jr., and Givner, I.: Diplobacillus of Petit in Corneal Ulceration: Report of Cases, Arch. Ophth. **25**:280, 1941.

as a cause of severe acute conjunctivitis, similar to a blennorrhea. Infections are commoner during the hot and dusty seasons of the year. Under various names, diplobacillary infections have been identified in many reports of hypopyon keratitis. Although Thygeson [9] reported only 6% in the United States, and Rhodes [13] 3% in Scotland, we found it to be the cause in 84% of our hospital admissions for hypopyon keratitis in the past two years. It has been reported from practically every country in the world and from practically every major city in North America.

PATHOGENESIS

Most authorities believe that the organism reaches the eye from a reservoir in the upper respiratory passages. It must be borne in mind that the morphology of the organisms when present in the nose may vary from that of organisms which occur in the eye. Duke-Elder [4] stated that Collins was one of the earliest to report the bacillus in the eyes and nose together, although earlier Briard had reported it in the nose. The infection may travel in retrograde fashion along the nasolacrimal passages, or more likely may be carried to the eyes by handkerchiefs or soiled fingers. Steen and Berdal [14] described chronic rhinosinusitis caused by Moraxella liquefaciens. The slight alkalinity of the tears is conducive to growth of the organism. However, as pointed out by Duke-Elder, there is something in the tears which checks the activity of this bacillus. This substance does not appear to be lysozyme, according to a report by Thompson.[15] It is more likely an antiprotease. The organism exists subclinically as a saprophyte on the surface of the epithelium, and apparently causes damage only when it becomes unusually virulent or the resistance of the host is decreased. Thus, the organism can live on the conjunctiva without causing any reaction there, but if the protease [16] which it elaborates reaches the unprotected skin at the canthi, it will digest the skin. Because of its relatively greater activity in the canthal region, it has earned the name bacillus of angular conjunctivitis. When the patient's resistance is lowered, the organism can cause a conjunctivitis of variable severity, which is chronic and indolent. This may be accompanied by shallow marginal corneal ulcers. We believe that if the patient is debilitated and neglectful, especially if trauma to the cornea is superimposed, then organisms from a nasal infection are capable of becoming directly invasive of the central cornea, to produce hypopyon keratitis. It has been suggested [9] that damage to the corneal epithelium is a prerequisite to the development of all central ulcers. This statement seems to be sound, but is difficult to prove in the poorly observant patients prone to this condition.

BACTERIOLOGY

When one is discussing the bacteriology of the Morax-Axenfeld bacillus, it is impossible to be dogmatic. It is well known in the field of bacteriology that micro-

13. Rhodes, A. J.: Studies on Bacteriology of Hypopyon Ulcer: Bacteriological Investigation of 120 Cases of Hypopyon Ulcer, Brit. J. Ophth. **23**:627, 1939.

14. Steen, E., and Berdal, P.: Chronic Rhinosinusitis Caused by Moraxella Liquefaciens Petit, Acta oto-laryng. **38**:31, 1950.

15. Thompson, R.: Lysozyme and the Antibacterial Property of Tears, Arch. Ophth. **25**:491, 1941.

16. Diplobacillus Protease and Effect of Sulphate of Zinc on Blepharoconjunctivitis Angularis, von Graefes Arch. Ophth. **116**:638, 1926.

organisms are capable of undergoing considerable variation, transgeneration, and dissociation. This variation can occur in size, shape, staining reaction, cultural characteristics, and pathogenicity. The variation may be permanent, but usually is a temporary or reversible response, induced by a change in the conditions under which the organisms must grow, and may be interpreted as being one of the most basic adaptive phenomena.

The bacillus is 1 to 1.5 μ broad and 2 to 3 μ long. The over-all size and shape of the organism vary, depending on the conditions under which it is growing. In culture, morphologic changes occur quickly. On examination the first or second day, one finds only diplobacillary or streptobacillary forms. But soon after involutional forms are found, and these may vary tremendously from long thin, filamentous forms, to short coccobacilli, and from Gram-negative to Gram-positive. They may be long and club-shaped, like corynebacteria, as in the Gram-positive Bacillus duplex of Joseph,[17] or they may be very short. Long filamentary forms usually stain a pale pink, whereas the short stout coccobacillary forms may be fairly Gram-positive. The organism generally assumes the former stain and shape in liquid media and the latter in solid media. The longer it is cultured on a solid medium, the more Gram-positive it becomes. The variations in this respect are so marked that in our laboratory we believe we may have demonstrated a linkage of this bacillus to the Micrococcus recently described by Mitsui and associates.[18] In vivo it is equally variable, and when recovered from cases of sinusitis and rhinitis it may show capsules, central vacuoles, ovoid bodies, and other features, making it practically indistinguishable from Klebsiella pneumoniae (Friedländer's bacillus).

Generally, it can be grown on any medium containing animal serum. Löffler's serum is one of the best, although Topley and Wilson[19] suggested Fildes' agar. Löffler's serum is certainly the most practical for the ophthalmologist. When grown on this, deep pits form. Confluence of the pits and liquefaction of the medium imply that a large number of organisms were deposited in the inoculation; it does not mean, as has been suggested, that one is growing the diplobacillus of Petit, rather than the Morax-Axenfeld bacillus. Axenfeld stated that his organism would not grow on blood agar. Since then, many investigators have grown it on this medium, especially in subculture, where it forms slightly mucoid colonies resembling Klebsiella, or Type III Pneumococcus. It will slowly liquefy gelatin at room temperature in two or three days. We had no growth on chocolate agar, although Elliot and associates[12] did. It can be grown on plain agar. Various investigators have grown either the diplobacillus of Petit or the Morax-Axenfeld bacillus on plain agar; therefore this characteristic cannot be used as a point of differentiation. It is important that any medium used should have an alkaline reaction. Micrococcus pyogenes var. aureus (Staphylococcus aureus), which produces an acid medium, inhibits the growth of the diplobacillus, corynebacteria, which produce an alkaline medium, enhance its growth. The organism is not very hardy and lives only a few days, even at incubator temperature on a favorable medium. In dried secretions

17. Scarlett, H. W.: Diplobacilli in Corneal Ulcers, Arch. Ophth. **46**:219, 1917.

18. Mitsui, Y.; Hinokuma, S., and Tanaka, C.: Etiology of Angular Conjunctivitis, Am. J. Ophth. **34**:1579, 1951.

19. Topley, W. C., and Wilson, G. S.: Topley and Wilson's Principles of Bacteriology and Immunology, Vol. 1, Ed. 3, Baltimore, Williams & Wilkins Company, 1946.

it can survive several days. In our laboratory, by repeated transfer, we were able to keep some cultures alive for almost three weeks. It is important to note that it is very difficult, and often impossible, to obtain growth on blood agar, or on plain agar, when one uses material obtained directly from the conjunctiva in known cases of Morax-Axenfeld conjunctivitis. However, when one uses subculture material from Löffler's medium, it is very easy to grow the organism on blood and plain agar. Unfortunately, the early writers did not state whether they used material directly from the eye or subcultured organisms.

The pathogenicity in animals is slight. Axenfeld [8] stated that the organism was not pathogenic for animals. Petit [1] stated that intralamellar inoculation of the rabbit cornea produced only a mild reaction, which lasted but four or five days. Elliot and associates [12] produced hypopyon in rabbits. Morax [20] was able to produce ocular infection in the chimpanzee. Oeding [21] produced proliferation in the peritoneum of the mouse but said that the organism later lost its virulence. The severest lesions occur in man, as the eye can be completely lost as a result of central abscess. In our laboratory we were able to produce conjunctivitis in the rabbit by subconjunctival injection, and were able to produce a small corneal abscess by intralamellar injection into the cornea of a sufficiently concentrated suspension of the organisms. Extensive work has not been done on immunologic response to the organism, and we made no study of this.

CLASSIFICATION

No classification set forth so far has been entirely satisfactory. Some are based on the presenting clinical picture; others, on the cultural characteristics, and others, on the morphology of various forms. Actually, all such factors are variable, and until a large number of observations have been made, with adequate control, no classification can be considered final. One of the most popular is that of Lwoff [22] which describes Genus II, Moraxella, of the tribe Hemophileae thus:

Species 1: M. lacunata (Morax-Axenfeld bacillus)
Species 2: M. liquefaciens (diplobacillus of Petit)
Species 3: M. bovis (a cause of "pinkeye" in cattle)

Actually, organisms thought to be the diplobacilli of Petit form lacunae in Löffler's medium, and organisms thought to be Morax-Axenfeld bacilli can liquefy gelatin and coagulated serum, so that this classification cannot be considered satisfactory.

PATHOLOGIC PICTURE

In cases of conjunctivitis the organism is very easily found. It is extremely plentiful in scrapings or smears of secretion from the angle, lying free or on epithelial cells, but not in them. Numerous strands of fibrin are characteristic. Since the exudate is rich in fibrin, the organisms usually are caught up in the strands; and since both components take a similar pink stain, the organisms are difficult

20. Morax, V.: L'infection diplobacillaire, Ann. ocul. **169**:81, 1932.

21. Oeding, P.: Diplobacillus Liquefaciens of Petit Isolated from a Patient with Ulcus Serpens Corneae: Description of Microbe with Historical Survey and Discussion on Classification of Diplobacilli, Acta ophth. **24**:159, 1946.

22. Lwoff, A.: Revision et démembrement des Hemophilæ: Le genre Moraxella nov. gen., Ann. Inst. Pasteur **62**:168, 1939.

to identify at first. Their size varies considerably; although the ends are typically rectangular, the diplobacilli may have rounded ends, which at times may be slightly swollen and stain more intensely.

In cases of keratitis, one must scrape deep, since the bacilli are at the base of the ulcer, not at the margin, as in cases of pneumococcic ulcer. The process tends to go deep, and intracorneal abscess is a characteristic finding. Early investigators described two infiltrated zones in many cases. One was about the ulcer itself, and the second, separated from the first by a layer of clear stroma, was situated deeper. The more posterior infiltration may lead to formation of a posterior abscess. This second area of corneal weakening tends to make it easier for descemetocele to develop. The peripheral lamellae of the cornea show little or no necrosis. Sections of the slowly deepening ulcer will show infiltration with lymphocytes, plasma cells, mononuclear cells, and occasional polymorphonuclear leucocytes. There is often a collection of fibrinous material in the crater. The hypopyon at first consists mostly of lymphocytes, but, as time goes on, it becomes firm and coherent as it is knit together by the tightening strands of fibrin. The fibrin meshwork contains some red blood cells and a few polymorphonuclear leucocytes.

REPORT OF CASES

Case 1.—J. N., a debilitated white man aged 58, was admitted to Bellevue Hospital Feb. 26, 1951, with the history of a "sore eye" for two weeks. He said that this had come on with a cold. Vision was 16/30 in the right eye and was limited to light projection in the left. The left eye showed red edematous lids, injected edematous conjunctiva with considerable exudate, and a large ulcer involving the lower half of the cornea. Hypopyon was noted in the anterior chamber. The cornea was infiltrated deep to the ulcer, and there were folds in Descemet's membrane. Tension was not abnormal. Under treatment, the ulcer became inactive, and the patient was discharged, with a residual scar.

Case 2.—D. H., a debilitated white man aged 51, was admitted to Bellevue Hospital on July 9, 1951, with a three-day history of itching and moderate pain in the right eye. Vision was limited to light projection in the right eye and was 16/20 in the left eye. The right eye showed moderate edema of the lids, diffuse injection of the conjunctiva, and a large deep ulcer involving the lower half of the central portion of the cornea. There was a small hypopyon. There developed increased intraocular tension and a small area of ectasia in the central area of the abscess four days after admission. The ulcer became inactive, and he was discharged, with a residual scar, on Aug. 25.

Case 3.—D. S., a debilitated white man aged 58, was admitted to Bellevue Hospital on Sept. 11, 1951, with a history of mild pain and redness in the right eye for one week. He said he had had a severe cold at the time of onset. Vision in the right eye was limited to perception of hand movements at 1 ft. (30 cm.) and was 16/30 in the left eye. He had a slightly enlarged preauricular lymph node on the right side. There were diffuse conjunctival injection and slight chemosis of the right lids. A corneal abscess was present, extending through the deeper layers, and there was a large central descemetocele, covered with bloody exudate. Although poorly seen, the anterior chamber appeared to have hypopyon. Under treatment the ocular reaction subsided. However, extremely painful secondary glaucoma developed, and the eye had to be enucleated on Nov. 8.

Case 4.—L. B., a white woman aged 49 in poor general condition, was admitted to Bellevue Hospital on Nov. 8, 1951, with a two-week history of moderate pain in the right eye. She had moderate nasopharyngitis. Vision was equal to light projection in the right eye and was 16/50 in the left eye. The right upper lid was swollen, and the conjunctiva was diffusely red, chemotic, and covered with mucopurulent exudate. The anterior chamber was very shallow, and tension, as determined by finger palpation, was 4+. The central two-thirds of the cornea contained a grayish-yellow, deep abscess, and the rest of the cornea appeared edematous. Two days after

her admission a descemetocele formed and massive rupture occurred, with loss of vitreous. Evisceration was performed on Nov. 11.

Case 5.—B. L., a debilitated white man aged 50, was admitted to Bellevue Hospital on May 13, 1952, with the complaint of a "cold" in the right eye for three weeks, from which he had not recovered. Three days before his admission the condition had become worse and "some" pain developed. Vision was equal to light projection in the right eye and was 16/20 in the left eye. The right eye showed a small (3 mm.) central ulcer, with hypopyon. The iris was congested. There was chronic blepharoconjunctivitis of both eyes. The right eye was tender, and there was slight edema of the cornea. Although the eye improved, the patient still was in the hospital at the time of writing.

Case 6.—R. W., a debilitated white man aged 59, was admitted to Bellevue Hospital May 14, 1952, with the complaint of a "cold" in the right eye for three weeks. The eye had become painful two days before admission, and at that time he noticed he could not see well with it. Vision was equal to light projection in the right eye and was 16/30 in the left eye. The right eye showed a small central ulcer, with a large hypopyon. The pupil was fixed. The lids were inflamed and somewhat chemotic. The eye improved under treatment; then the patient had a relapse, still being in the hospital at the time of writing.

It is of interest to note that of these six patients, five freely admitted that they were chronic alcoholics.

BACTERIOLOGIC STUDY

In this study, organisms were recovered from unquestionable cases of Morax-Axenfeld conjunctivitis and were compared with organisms from our cases of hypopyon keratitis to see whether there was any bacteriologic basis for the belief that conjunctivitis must be due to the Morax-Axenfeld bacillus and central hypopyon ulcer to the diplobacillus of Petit. The organisms were compared in direct smear, in culture, and in animal pathogenicity. In the cultural study, inoculations were made from the eye to Löffler's coagulated blood serum-dextrose medium, blood agar, and plain agar; subcultures were made from the colonies on Löffler's serum to plain agar, blood agar, serum broth, and gelatin, and from the serum broth back to blood agar. In Case 4 studies also were made of material from the nose. In none of these studies of any of our cases were signficant differences found between the organisms recovered from the cases of conjunctivitis and those recovered from the cases of central hypopyon ulcer.

For the study of organisms causing conjunctivitis, recourse was had to a psychiatric institution where diplobacillary conjunctivitis is endemic. Eleven patients had material cultured. Nine of these cultures showed contamination with staphylococci; therefore only the two pure cultures were used. Our purpose in subculturing the serum broth to blood agar again was to demonstrate the morphologic changes which occur and to prove the absence of contamination, in the face of the great variations found in the serum broth culture. The same cultures were used throughout, and the organisms were never exposed to any antibiotics, in vivo or in vitro.

TREATMENT

Treatments for infections with the diplobacillus are legion. Zinc is specific, equally for the diplobacillus of Petit and the Morax-Axenfeld bacillus. It must be used in fairly high concentrations to be effective. Thygeson,[23] in discussing the

23. Thygeson, P., in Berens, C.: The Eye and Its Diseases, Ed. 2, Philadelphia, W. B. Saunders Company, 1949.

treatment of conjunctivitis, advised use of a 0.25% solution of zinc sulfate four times a day and of a 0.5% ointment twice a day. He stated that this therapy must be given for several weeks, and that failure is due to mixed infection with staphylococci, for which he advocated concurrent sulfonamide therapy. One of us (H. F.) has used zinc sulfate in as high as 25% concentration in the successful treatment by chemical cautery of corneal ulcers. Gifford [24] used a 20% solution. Elliot and associates,[12] used a 0.5% solution four times a day, with 0.5% ointment at night, in addition to their other therapy. We used zinc sulfate by iontophoresis, in 1% solution for two minutes at 2 ma. once or twice a day. Irrigation of the sacs is an important procedure and may be done with solutions of zinc sulfate or antibiotics.

Most of the older writers are in favor of opening the cornea, by a Guthrie-Saemisch section, Sondermann trephination, delimiting keratotomy, or their own favorite mode of section. This is believed to have a twofold purpose: first, to reduce the tension in the anterior chamber, for it is known that ocular hypertension delays ulcer healing, and, second, to bring in the secondary aqueous. With regard to the latter effect, one must remember that the formation of immune bodies as a result of central corneal ulcer has never been shown to be impressive. Such surgical procedures are in themselves not without danger and can result in iris prolapse, cataract, and other such complications.[25]

Oeding [21] stated that the diplobacillus of Petit was susceptible in vitro to 0.01 Oxford unit of penicillin. The intramuscular use of penicillin was not impressive in our cases. We also used streptomycin, chloramphenicol, aureomycin, and neomycin as topical antibiotics and applied the chemotherapeutic agents sulfisoxazoline (gantrisin®) and sulfathiazole. The most dramatic clearing of the inflammatory reaction was noted with the use of chloramphenicol. We also used the agents streptokinase and streptodornase in the last two cases, to help clear the fibrin and debris from the ulcerated surface. The effect of these enzymes on healing cannot yet be determined.

Application of heat in various forms, from hot compresses to the thermophore, and even the actual cautery, has been used for these ulcers. None of these have proved consistently effective.

Supportive measures are of considerable importance. These include bed rest; nutritious diet; use of vitamins, when indicated by the debilitated, and the removal of foci of infection. One may give salicylates, employ foreign protein therapy, and administer atropine topically. An attempt should be made to rid the nose and throat of the organisms if possible, in order to obviate the possibility of reinfection from that source.

Sterilization of the lesion with the proper antibiotics, unfortunately, does not result in complete cure. Even when the eye has been rendered free from the responsible organism, the structural damage and complications, such as corneal opacity, descemetocele, and secondary glaucoma, frequently result in irretrievable loss of vision. If the progress of the ulcer is halted early enough, and only the cornea suffers, sometimes surgical therapy, such as corneal transplantation, may restore useful vision.

24. Gifford, S.: Ulcer of Cornea, Am. J. Ophth. **4**:460, 1921.

25. von Sallmann, L.: Über Komplikationen bei der Sondermannschen Trepanation des Ulcus serpens, Ztschr. Augenh. **60**:284, 1926

CONCLUSIONS

1. The differentiation of hypopyon keratitis caused by Gram-negative diplobacilli into two types, one supposedly due to the diplobacillus of Petit and the other to the Morax-Axenfeld bacillus, on either clinical or bacteriologic grounds is not well founded. In the first the clinical picture does not depend upon the infecting type of organism, but, rather, is the result of local differences between the central and the peripheral portion of the cornea and the general constitution of the patient. It can be demonstrated that bacilli recovered from either type can be made to show the same cultural reactions, growth characteristics, morphologic pattern, and degree of animal pathogenicity.

2. In most cases of central corneal ulcer with hypopyon seen at Bellevue Hospital the infecting organism is a Gram-negative bacillus, especially the Morax-Axenfeld bacillus. This is in contrast to the high incidence of pneumococcic ulcers reported elsewhere. We believe this predominance is due to the debilitated condition of our patient population.

3. Present classifications of the Gram-negative diplobacilli are unsatisfactory, as they retain an ill-founded division into two artificial groups and fail to account for the many variations which occur.

Miss Tucharsky and Mr. T. Riordan gave technical assistance.

EFFECT OF SULFONAMIDES AND ANTIBIOTICS ON PANOPHTHALMITIS COMPLICATING CATARACT EXTRACTION

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IN MANY fields of medicine and surgery, the sulfonamides and antibiotics have greatly reduced the frequency and severity of infections and have altered the types and the strains of responsible micro-organisms. It has been the purposes of this study (1) to ascertain whether the use of these compounds and preoperative cultures of the conjunctivae and lids have reduced the incidence of panophthalmitis following cataract extraction, (2) to learn whether the type of organism responsible has been changed by the use of these substances, and (3) to discover whether vision and the globes that nevertheless have become involved with panophthalmitis after cataract extraction have been salvaged by their use. I have used for material a series of 1,653 cases of cataract extractions composed of my private cases and the charity cases in which extractions were performed by members of the attending staff and resident staff of the Hillman (University of Alabama) Clinic at the Thigpen-Cater Eye Hospital from September, 1947, through August, 1952. In each of these cases cultures of material from the lids and conjunctivae were taken at the time of admission to the hospital, 40 to 48 hours before the scheduled operation.

In most of the comprehensive studies of the complications of large series of cataract extractions that have been published in the last two decades,[1] a detailed bacteriologic investigation of operative infections has not been included. Exceptions are the articles by Berens and Bogart,[1] 1938; Dunnington and Locatcher-Khorazo,[2] 1945; Dellaporta, Riemer, and Harmouth,[3] 1945, and Pulvertaft,[4] 1949 (Table 1).

The effect of sulfonamides and antibiotics was considered only in the articles of Dunnington and Locatcher-Khorazo,[2] and Dellaporta, Riemer, and Harmouth.[3]

In the latter part of the studies of Dunnington and Locatcher-Khorazo the effect of sulfonamides and antibiotics was related to the susceptibilities of the various

From the Medical College of Alabama.

1. Berens, C., and Bogart, D.: Certain Postoperative Complications of Cataract Operations, with Special Reference to 1,004 Operations, Am. J. Surg. **42**:39-61, 1938.

2. Dunnington, J. H., and Locatcher-Khorazo, D.: Value of Cultures Before Operation for Cataract, Arch. Ophth. **34**:215-219, 1945,

3. Dellaporta, A.; Riemer, F., and Harmouth, E.: Comparative Study of Frequency of Infections Following Cataract Operations During Years 1936, 1941, 1946 and 1948, with Special Considerations of Penicillin Therapy, Klin. Monatsbl. Augenh. **115**:369-383, 1949.

4. Pulvertaft, R. J. V., and others: Discussion: Principles and Practice of Asepsis in Ophthalmic Operations, Tr. Ophth. Soc. U. Kingdom **69**:355-395, 1950.

micro-organisms. Staphylococcus aureus was found to be the micro-organismal cause of the panophthalmitis in all 11 eyes. From their studies, they concluded that the incidence of infection was unrelated to intracapsular or extracapsular methods.

Dellaporta and associates compared the operative infections after cataract extraction at the First University Eye Clinic in Vienna for 1936, 1941, 1946, and 1948. They related the higher loss of infected eyes in 1946 to poor nutrition of the populace and expressed the belief that the lowered incidence in 1948 was due to the prophylactic use of penicillin. From their studies they concluded that the

TABLE 1.—*Panophthalmitis Complicating Cataract Extraction; Series Reported in the Literature of 1921 to 1952, Including Our Own*

Author	No. of Cases	Panophthalmitis	
Bell (1921)	400	2 (0.5%)	
Maller (1923)	249	2 (0.8%)	
Girl (1923)	384	6 (1.5%)	
Parker (1927)	150	1 (0.66%)	
	150	1 (0.66%)	
	150	1 (0.66%)	
Davenport (1928)	2,368	20 (0.88%)	
Slocum (1933)	882	9 (1.03%)	
Parker (1934)	100	1 (1%)	
	100	1 (1%)	
	100	1 (1%)	
Beach (1936)	100	1 (1%)	
Berens and Bogart * (1938)	702	1 (0.14%)	Extracapsular; intracapsular
	392		
Total	6,137	66 (0.75%)	
Pulvertaft † (1927-1941)	719	6 (0.8%)	Cultures in all cases
	1,841	10 (0.5%)	No cultures
Dunnington and Locatcher-Khorazo (1945)	2,508	11 (0.23%)	
Dellaporta and others			
1938	300	3 (1%)	
1941	401	2 (0.5%)	
1946	515	5 (1%)	
1948	509	0 (0.0%)	
Total	1,725	10 (0.6%)	
Wills Eye Hospital † (1944-1951)	4,000	6 (0.2%)	
Callahan ‡ (1947-1952)	1,653	5 (0.3%)	

* The tabulation of the 1921-1938 reports was assembled by Drs. Berens and Bogart and is reprinted with their permission.
† This summary was presented through the courtesy of Dr. Carrol Mullen.
‡ Details are presented in Table 2.

incidence of infection was much greater after the extracapsular method than after the intracapsular method of extraction.

Guyton and Woods [5] (1943) reported that the prophylactic oral use of sulfadiazine lowered significantly the incidence of postoperative infection. They used this drug in 312 cases and found the incidence of infection much less than in a larger series in which it was not used. After their report, however, they discontinued the use of sulfadiazine because of the danger of untoward side-effects, and with one-eyed patients or with patients who have any trace of preoperative infection of the conjunctiva or lid, they use prophylactic antibiotics.[6]

5. Guyton, J. S., and Woods, A. C.: Oral Use of Prophylactic Sulfadiazine for Cataract Extractions, Am. J. Ophth. **43**:1278-1282, 1943.

6. Guyton, J. S.: Personal communication to the author.

INCIDENCE OF PANOPHTHALMITIS IN PRESENT SERIES

Our incidence of panophthalmitis which developed without known breaks in aseptic technique, despite our routine preoperative culture study, is summarized on the last line of Table 1 and is presented in more detail in Table 2. The over-all incidence is 0.3%, or 5 eyes lost in a total of 1,653. The cataractous lenses in all these eyes were removed from beneath a limbus-based flap, and in most instances through a round pupil, without rupture of the lens capsule.

As is explained in the following section, the cases of infection in 1951 and 1952 would not have occurred had the respective cultures been given greater attention. In all the cases in which preoperative pathogenic micro-organisms were obtained on culture operation was delayed a period varying from two days to two weeks. During this time the patients were given special antibiotic treatment, and in no case was operation performed until sterile cultures from the lid and conjunctiva were obtained. In none of these cases of delayed operation did an infection develop.

TABLE 2.—*Panophthalmitis Complicating Cataract Extractions Done Without Known Breaks in Aseptic Technique at the Thigpen-Cater Eye Hospital*

	Sept.-Dec. 1947	1948	1949	1950	1951	Jan.-Aug. 1952	Total
No. cataract extractions	86	289	358	344	351	225	1,653
Infections							
No.	1	2	0	0	1	1	5
Per cent	1.6	0.65	0.00	0.00	0.28	0.44	0.3
Cases in which extraction was postponed because of growth of pathogenic micro-organisms from cultures	7	45	62	55	60	31	260
				(about ¼ of these were postponed because of cultures of Gram-negative bacilli)			

ETIOLOGY IN MY CASES OF PANOPHTHALMITIS (TABLE 3)

Micro-organisms which my bacteriologic colleagues and I considered pathogenic at the beginning of this study were as follows: (1) Streptococcus of the viridans type; (2) hemolytic Streptococcus; (3) M. pyogenes var. aureus (Staph. aureus), and (4) Diplococcus pneumoniae. In cases in which the cultures showed any of these pathogens on the lids or conjunctivae of the eye to be operated on, the extraction was postponed.

Indicated antibiotics were administered locally and systemically in large doses, and cultures were repeated every 48 hours. The operation was performed as soon as cultures negative for these pathogenic organisms were obtained. If these pathogens were present on the opposite lid or conjunctiva, extraction was performed as scheduled, and a wide spectrum range of indicated antibiotics were administered locally and systemically in large doses.

At first the presence of Gram-negative bacilli was not considered by us a contraindication to surgery. It was suspected in the aftermath study of the first eye lost (W. K.). Identification of the micro-organism responsible for the loss of the second eye (A. W. W.) confirmed the suspicion, and from then on we postponed the operation when these micro-organisms were present and gave local and systemic treatment until sterile cultures could be obtained.

TABLE 3.—*Data on My Series of Five Cases of Panophthalmitis Complicating Cataract Extractions*

Patient	Date	Preoperative Culture	Operation	Post-operative Day of Infection	Postoperative Culture	Local Treatment	General Treatment	Result	Date
W. K.	12/19/47	Gram-negative bacillus, unidentified	Extracapsular	2d	No culture	Anterior chamber irrigated twice with penicillin-streptomycin mixture	I. v. typhoid vaccine, i. m. penicillin	Enucleation	6/25/48
A. W. W.	8/ 9/48	(P. vulgaris) and Staph. albus, present on both pairs of lids	Intracapsular	4th	Staph. aureus; Gram-negative cocci	Penicillin solution injected subconjunctivally every 6 hr. 4 times and anterior chamber irrigated with penicillin solution once	I. v. typhoid vaccine; i. v. typhoid toxoid; oral sulfadiazine	Iridencleisis for occluded pupil; vision H. M. at 2 ft.; mild secondary glaucoma, controlled by mioties	9/27/51
H. G.	8/16/48	Staph. albus L. L. & R. L. Diphtheroids L. C.	Intracapsular	1st	A. aerogenes	Anterior chamber irrigated with streptomycin solution and penicillin ointment to lids	I. m. penicillin	Light perception	8/16/49
A. M. M	8/27/51	Gram-neg. rod L. L. & L. C. A. aerogenes Diphtheroids R. L.	Intracapsular	2d	Ps. aeruginosa	Chloramphenicol, iontophoresis, and sulfonamide drops instilled frequently; aureomycin ointment to lids	I. m. penicillin and streptomycin	Evisceration	8/31/51
T. P. R.	3/24/52	P. vulgaris R. C., (not reported until after surgery perf.) Diphtheroids R. L. and L. L., R. L.	Intracapsular	3d	P. vulgaris	Chloramphenicol, iontophoresis and as drops instilled frequently into conjunctival sac	Oral chloramphenicol, large doses	Enucleation	6/15/52

Our explanation of the loss of the third eye (H. G.) is that the pathogen must have been missed when the culture material was taken. Other cataract extractions performed the same day, with the same instruments, supplies, and personnel, were not followed by infection. In the case of the fourth eye lost (A. M. M.) a resident misunderstood our routine in cases in which Gram-negative bacilli are present and proceeded to operate on the patient. In the case of the fifth eye (T. P. R.) our bacteriologic colleague failed to note the presence of Proteus vulgaris at the time the culture plate was read but found one colony 60 hours after it was made, or 40 hours after the extraction was performed.

ROUTINE PREOPERATIVE ASEPTIC PROPHYLAXIS NOW IN USE

As can be understood, the loss of these five eyes from infection with Gram-negative organisms has caused a modification of our prophylaxis and has resulted in redoubled efforts to avoid infections. The routine procedure which we use for all cataract extractions is as follows:

1. For a week prior to operation the patient instills a small amount of polymyxin B-bacitracin (polysporin®) ophthalmic ointment inside each lower lid every night. Wiggins [7] reported that polymyxin B is effective against Gram-negative organisms, and Bradley [8] suggests polymyxin B-bacitracin ointment as a satisfactory routine prophylactic agent.

2. At the time of admission, 40 to 48 hours prior to operation, material from all lid margins and the conjunctiva of both eyes is plated on blood and milk agar. Milk plates facilitate more rapid identification of Staph. aureus, because the golden pigment is more readily discernible. A sterile cotton-tipped applicator is rubbed thoroughly against the conjunctiva of each eye separately and the material plated on each medium on marked areas. Other sterile cotton-tipped applicators are rubbed thoroughly on the lid margins, and vigorously wherever there is any clinical evidence of blepharitis or increased vascularity. The cultures are reported on by a bacteriologic colleague immediately before operation, which is about 40 hours after the time of the initial plating.

3. If any colonies of hemolytic Streptococcus, Streptococcus of the viridans type, Staph. aureus, and D. pneumoniae are found to grow from the conjunctiva of the eye to be operated on, the operation is tentatively rescheduled for two days later, but the patient is kept in the hospital and given intensive local and systemic antibiotic treatment. The eye is not operated upon until the cultures are free from pathogenic micro-organisms, and cultures are repeated every 48 hours. If any of these micro-organisms are found in large numbers on the lids of the eye to be operated on, the same routine is followed. If, however, only a few are present on the lid, or are present only on the conjunctiva or lid of the fellow eye, the operation is performed as scheduled, but large doses of the antibiotic substances indicated are given intramuscularly immediately and continued for four days. We believe this is a safe procedure, because these organisms are very sensitive to antibiotics.

4. If any colonies of P. vulgaris or other Gram-negative bacilli are found to grow from the conjunctiva or the lids of either eye, the operation is tentatively

7. Wiggins, R. L.: Experimental Studies of the Eye with Polymyxin B, Am. J. Ophth. **35**:83-99 (May, Pt. 2) 1952.

8. Braley, A. E.: Personal communication to the author.

TABLE 4.—*Published Reports of Treatment of Panophthalmitis Following Cataract Extraction*

Author	Extracapsular or Intracapsular	Postoperative Day Signs of Panophthalmitis	Organism Cultured	Local Treatment	General Treatment	Final Vision
Ainslie [9a] (1946)	?	8th; Nonunion of corneal wound	No culture	Some solid penicillin powder applied to eye	?	Light perception
Feigenbaum and Kornbluth [9b] (1945)	E	8th	Fluid and exudate from anterior chamber cultured, no growth, infection possibly endogenous	Anterior chamber repeatedly irrigated with penicillin	I.m. foreign protein; i.m. penicillin; oral sulfadiazine	20/200
Schneider and Frankel [9f] (1947)						
Case 1	E	7th	Staph. aureus	Anterior chamber injected with penicillin	I.v. and i.m. foreign protein; i.m. penicillin	Light perception; poor light projection
Case 2	E	11th	Staph. aureus	500 units penicillin injected in vitreous 13 days after infection showed	I.m. penicillin; oral sulfadiazine	Light perception; poor light projection
Lavery [9e] (1948)	E	4th	No culture	Subconjunctival injection, 500,000 penicillin; penicillin solution instilled	I.m. penicillin; oral sulfadiazine	20/20
Kravitz and Duest [9d] (1944)						
Case 1	E	5th	Smear negative; infection endogenous, authors' report	Sodium sulfathiazole solution, 5%, instilled every 2 hr.	Oral sulfadiazine; general supportive treatment	20/40+
Case 2	E	5th	Smear negative; infection endogenous, authors' report	Atropine sulfate, 1%; hot compresses; infrared therapy directly to eye	I.v. typhoid vaccine; i.m. sterile milk; oral sulfathiazole	20/10
Heinz [9c] (1948)	I	....	.....	Anterior chamber rinsed out with Ringer's solution	Collapsed eyeball rinsed and refilled with azosulfamide	6/12
Leopold [13] (1952) *						
Case 1	E	After 24 hr.	Ps. aeruginosa in aqueous	Penicillin 1 million U. subcutaneously once daily; polymyxin, 250 mg./0.2 cc. in anterior chamber	Oxytetracycline, 0.5 gm. every 6 hr. intramuscularly	Evisceration
Case 2	E	After 24 hr.	Aqueous, sterile	None	Chloramphenicol, 3 gm. stat; 0.5 gm. every 6 hr.	6/15
Case 3	E	After 24 hr.	No cultures	None	Chloramphenicol, 3 gm. stat; 0.5 gm. every 6 hr.	6/20
Case 4	I	After 24 hr.	Aqueous sterile	Penicillin, 1 million U., 0.5 cc. daily for 3 days; streptomycin, 50,000 U., 0.5 cc. subcutaneously once daily for 2 days	.....	Evisceration
Case 5	I	After 24 hr.	Aqueous sterile	Oxytetracycline, 250 mg./0.2 cc. into anterior chamber; penicillin 1 million U., 0.5 cc. subcutaneously once daily for 2 days	.....	6/15

* In four of these five cases penicillin or streptomycin was given intramuscularly before operation.

rescheduled for two weeks later, and the patient is dismissed from the hospital. We fear these organisms more than the Staphylococcus or Streptococcus because they are less sensitive to antibiotics. Polymyxin B-bacitracin ointment is applied to both lids three times a day, and chloramphenicol is given by mouth. Cultures are made every few days, but, in our experience, two to three weeks is frequently required to obtain a culture free from Gram-negative bacilli.

Immediately preceding the operation, the lids and orbital regions are scrubbed thoroughly with one of the cocoanut-oil antiseptic derivatives, such as pHisoderm with hexachlorophene (pHiso Hex®), irrigated with sterile saline, and tincture of benzalkonium (zephiran®) chloride applied to the surgical field.

ANTIBIOTIC THERAPY OF PANOPHTHALMITIS FOLLOWING CATARACT EXTRACTION

Despite every precaution, panophthalmitis may follow cataract extraction. Published reports [9] on the efforts to salvage such eyes show that the prognosis is very poor (Table 4).

Of the 12 eyes reported in the literature, the etiologic micro-organism was successfully cultured in only 3. If it could have been identified in the other nine, the treatment might have been more specific and the end-results better.

Of our five cases, the organism was identified in four, but in only two of these was the globe salvaged, and useful vision was not saved in either eye. There will be a greater chance of saving eyes infected with Gram-negative bacilli when a more effective antibiotic for these organisms is developed.

Recommended Management.—The patient with panophthalmitis following cataract extraction has a greater chance of recovery if the surgeon will immediately perform a paracentesis, collect the aqueous for culture, and lavage the anterior chamber with a combination of wide-spectrum antibiotics.

Leopold's [10] recent report indicates that oral administration of chloramphenicol (3 gm. at once and 1 gm. every six hours) is the best method of systemic treatment presently available. Many studies [11] have shown that intramuscular injections of penicillin and streptomycin are of no value in such conditions because the intraocular level of these substances cannot thereby be sufficiently elevated. It is easier to inject penicillin and/or streptomycin into the anterior chamber or beneath the conjunctiva than it is to use these substances intravenously, and they are much more effective when used directly in the eye.

9. (*a*) Ainslie, D.: Use of Solid Penicillin in Case of Endophthalmitis Following Lens Extraction, Brit. J. Ophth. **30**:208, 1946. (*b*) Feigenbaum, A., and Kornblüth, W.: Intravitreal Injection of Penicillin in Case of Incipient Abscess of Vitreous Following Extracapsular Cataract Extraction Perfect Cure; Report of Case, Ophthalmologica **110**:300-305, 1945. (*c*) Heinz, K. H.: Cure of Infection After Cataract by Removal of Infected Vitreous Body and Washing Out of Vitreous Cavity with Prontosil (Azosulfamide), Wien. klin. Wchnschr. **60**: 87, 1948. (*d*) Kravitz, D., and Duest, L. J.: Postoperative Endogenous Infection of Eye with Recovery: Report of 2 Cases, Am. J. Ophth. **27**:167-171; Correction **27**:303, 1944. (*e*) Lavery, F. S.: Postoperative Intra-Ocular Infection Controlled by Penicillin, Brit. J. Ophth. **32**:247, 1948. (*f*) Schneider, J., and Frankel, S. S.: Treatment of Late Postoperative Intraocular Infections with Intraocular Injection of Penicillin, Arch. Ophth. **37**:304-307, 1947.

10. Leopold, I. H.: Surgery of Ocular Trauma, A. M. A. Arch. Ophth. **48**:738-746, 1952.

11. Leopold, I. H.: Intravitreal Penetration of Penicillin and Penicillin Therapy of Infections of the Vitreous, Arch. Ophth. **33**:211, 1945. Sorsby, A., and Ungar, J.: Control of Experimental Infection of the Vitreous by Penicillin, Brit. J. Ophth. **34**:645, 1950.

The role of cortisone in the control of intraocular infection is not yet clearly established; it may block the penetration of some of the antibiotic agents through the blood-aqueous barrier.[11]

If an antibiotic appears to be unsuccessful in controlling the infection after a 24-hour period, another antibiotic should be tried.

COMMENT

At only a few of the ophthalmic hospitals in the United States are cultures from the lids and conjunctiva now made before cataract extractions as a routine preoperation measure. At most, cultures are made only in cases in which clinical signs of conjunctivitis or blepharitis are exhibited, and even in a large medical center such cases may be only a few a year. Ophthalmic surgeons delay the operation if there is clinical evidence of conjunctivitis, but only a few make preoperative cultures on all their cataract patients. Many ophthalmologists prescribe one of the ophthalmic antibiotic ointments routinely for a week or two before surgery.

As Maumenee [12] has stated, it is paradoxical that, despite the advance of knowledge of asepsis and experience with antibiotics and sulfonamide compounds, intraocular infections still occur. He has suggested as the explanation that the surgical procedure is now much longer and the technique more complicated.

SUMMARY AND CONCLUSIONS

The use of the antibiotics and preoperative cultures of material from the conjunctiva and lids have reduced the incidence of panophthalmitis following cataract extraction, but the complication still occurs in every large series despite every precaution now known.

Panophthalmitis caused by the hemolytic Streptococcus, Streptococcus of the viridans type, M. pyogenes var. aureus (Staph. aureus), and D. pneumoniae is more likely to be controlled with antibiotics now available than it was formerly. It is likely that the type of organisms responsible for panophthalmitis is changing, since this paper and the one by Leopold [11] are among the first to report Gram-negative bacilli.

The Gram-negative bacilli of the coliform group, normally present in the intestinal canal, are occasional contaminants of the conjunctivae and lids. In some cases these micro-organisms become virulent upon reaching the vitreous and cause the loss of the eye. In each of the five cases in which the eye was lost, clinical examination before operation showed no conjunctivitis or blepharitis. In the future, perhaps similar eyes may be saved by a more specific antibiotic.

We believe that preoperative cultures have saved a number of our cases. In about one-fourth of the 260 cases in which cataract extraction was postponed because of growth on cultures, Gram-negative bacilli were obtained, and we believe that some of the eyes would have been lost if operation had been performed at the first scheduled date.

The prognosis for salvage of the globe and vision when panophthalmitis has developed is very poor despite the use of antibiotics and sulfonamides.

Dr. Charles Winkler and Mrs. Louise Cason, of the Department of Bacteriology, Medical College of Alabama, assisted in this study.

12. Maumenee, A. E., and Michler, R. C.: Sterility of the Operative-Field After Ocular Surgery, Tr. Pacific Coast Oto-Ophth. Soc. **32**:172-183, 1951.

Registry of Interesting Cases

It is the purpose of this section to record cases on the basis of interest only. No complete review of the literature is attempted and no claim for priority is implied except when specifically stated. Publication of case reports is subject to the concurrence of the Editorial Board on the interesting aspects of the case. It is requested that the reports submitted be as brief as is consistent with inclusion of the pertinent facts, bear a title that is as specific as possible, be prefaced by a paragraph that states why the author feels the case is of interest and be accompanied with photographs whenever possible.

CUTIS HYPERELASTICA (EHLERS-DANLOS SYNDROME) WITH BLUE SCLERAS, MICROCORNEA, AND GLAUCOMA

CUTIS hyperelastica (Ehlers-Danlos syndrome[1]), also known as dermatorrhexis, or rubber skin, is characterized by the following: 1. Hyperelasticity of the skin. The skin possesses a rubber-like consistency, shown in its ability to retract after being pulled out at least 5 to 6 in. (12.5 to 15 cm.). The retraction is complete and devoid of wrinkles and folds. 2. Hyperlaxity of the joints. 3. Fragility of the skin, usually the chief and most obvious sign, involving especially the exposed surfaces and prominences, where scars are often evident. The scars are characteristically cigaret-paper-like areas. 4. Pseudotumors following trauma.

While isolated cases exhibiting one or more of these characteristics have been described, the complete syndrome rarely occurs.

The interest in the present case is the association of the dermatological condition of the Ehlers-Danlos syndrome with blue scleras and microcornea. These may all have occurred on the basis of a congenital defect in collagenous tissue, while the glaucoma was probably a result of the microcornea, which produced a congenital defect in the outflow mechanism of the aqueous humor.

REPORT OF A CASE

Mrs. I. L., aged 27, was first seen in April, 1950, with the complaint of periodic attacks of blurring of vision for both distance and near, dizziness, halos around lights, nausea, and headaches. Examination revealed bilateral microcornea and pronounced epicanthus, with a bluish tint to the sclera, especially above the level of the ora serrata (Fig. 1). The intraocular pressure measured 42 mm. Hg in each eye. Pilocarpine nitrate, 2%, reduced the pressure to within normal limits and eliminated the headaches, halos, and nausea.

The cornea measured 8.5 mm. in the right eye and 9 mm. in the left eye. The blue sclera in each eye had the appearance of a staphyloma between the insertion of the superior and medial rectus muscles, but the sclera in these regions was only thin, and did not bulge. Numerous vitreous opacities were seen in a highly myopic fundus. A central cup, with the vessels pushed to the nasal side, was noted in each eye. Vision was corrected to 20/40-2 and Jaeger Type 3 in the right eye with a correction of —9.50 sph. ⌒ +2.25 cyl., axis 5, and 20/25 and Jaeger Type 1 in the left eye with a correction of —11.75 sph. ⌒ +3.25 cyl., axis 5.

The dermatological picture presented many of the features described as characteristic of the Ehlers-Danlos syndrome. Hyperelasticity of the skin (Fig. 2*A*), hyperlaxity of the joints (Fig. 2*B*), and scars of the exposed portions of the legs (Fig. 2*C*) were all present. No pseudotumors from trauma were noted. In addition, scoliosis had been present since birth.

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1. Duke-Elder, W. S.: Text-Book of Ophthalmology, Vol. 5: The Ocular Adnexa, St. Louis, C. V. Mosby Company, 1952, p. 4674.

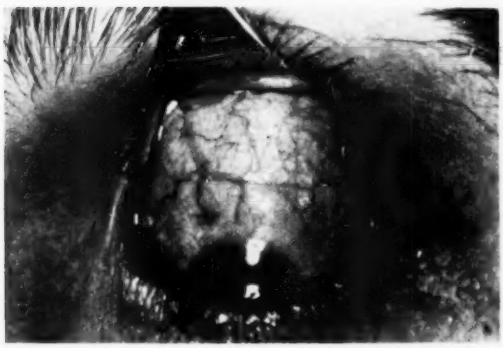

Fig. 1.—Microcornea, epicanthus, and bluish tint to the scleras above the ora serrata.

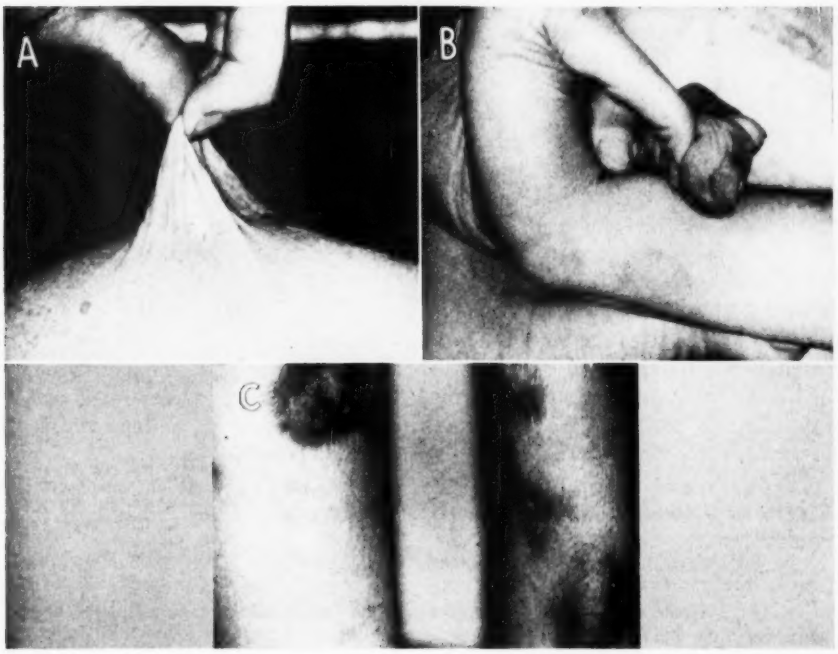

Fig. 2.—*A*, hyperelasticity of the skin; *B*, hyperlaxity of the joints; *C*, pigmented scars on exposed portions of the legs.

Annual Reviews

CORNEA AND SCLERA

Review of the Literature

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ANATOMY AND EMBRYOLOGY

ONE OF the very few studies concerning the embryology of the cornea to appear in the past year is presented by de Vincentiis and Auricchio [1] and concerns the metabolism of the cornea during embryonal life; the work was done on the chick embryo. They found that respiration in the cornea decreases from the 12th day of incubation to birth, that glycolysis diminishes slowly up to the 14th day, and that respiration and glycolysis rates are definitely more elevated in the first days of life than in the adult stage.

In 1950 Sebruyns [2] contributed his work on the ultrastructure of the cornea; he [3] has since done further work on the same subject and has added to our present knowledge. In this study he describes the print of the cells of the basal layer of the epithelium. This gives the appearance of a substance more or less homogenous, and completely full of round or oval vacuoles of different sizes, presenting a spongioid appearance. The ultrastructure of these cells is finer than that found in renal or hepatic cells. The vacuoles are arranged in more or less horizontal vacuolar trails. In the middle layer of the epithelium, the ultrastructure is found to be even finer, with smaller, more regular vacuoles. The superficial cells present a substance which is almost homogeneous and in which no vacuoles are found. In the cornea proper there is a typical disposition of the conjunctival fibrils. The tracts composing the fibrils have a spiral structure; they follow the longitudinal axis of the fibrils.

The importance of this work can be seen when the relation of it to the physiologic properties of the cornea is demonstrated. The construction of the epithelial cells of the cornea is such that the rays of light passing through them are minimally refracted. In addition, the helicoid molecular disposition of the conjunctival fibrils of the corneal tissue adds to the transparency of the cornea.

Several articles dealing with corneal innervation have appeared in the past year. The innervation of the cornea, as determined by Rodger,[4] is derived entirely from

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In this review, special attention is paid to pertinent material appearing in the literature from October, 1951, to October, 1952.

1. de Vincentiis, M., and Auricchio, G.: Metabolism of the Cornea and Lens During Embryonal Life, Rass. ital. ottal. **20**:69, 1951.

2. Sebruyns, M.: Ultrastructure of the Cornea and Lens Studied with the Electronic Microscope, Ann. ocul. **183**:483, 1950.

3. Sebruyns, M.: Ultrastructure of the Cornea and the Lens Studied with the Electronic Microscope, Am. J. Ophth. **34**:1437, 1951.

4. Rodger, F. C.: Some Observations on the Corneal Innervation, Tr. Ophth. Soc. U. Kingdom **71**:687, 1951.

the ophthalmic division of the trigeminal nerve; most of the fibers are sensory, carrying only pain sensation. Sympathetic fibers are not present, although parasympathetic fibers may or may not be represented. The limbus is the site of entry of the nerves, which then divide twofold or threefold to form three plexuses, the last of which is subepithelial. From this, arcades are formed, whose free endings terminate between the epithelial cells. According to Zander and Weddell,[5] between 61 and 68 nerve bundles enter the cornea; half of these contain between 15 and 30 axons, with fewer for the other half. An episcleral pericorneal plexus is formed from the deep bundles; the superficial layers of the substantia propria are supplied by this. The myelinated fibers which are found in the cornea do not extend farther than 2 mm. from the limbus.

Spadavecchia[6] asserts that, although the corneal innervation stems from both the autonomic system and the trigeminal nerve, the innervation is functionally single and indivisible. The physiologic and normal functioning of the cornea is therefore dependent upon centrifugal neurovegetative impulses and on antidromal trigeminal impulses, which arise either centrally or reflexly. The corneal sensation in the brain stem is represented along with the facial sensation of pain and temperature; the sensation of touch is not included.[7]

PHYSIOLOGY, PHARMACOLOGY, AND EXPERIMENTAL PATHOLOGY

In our modern age of advanced experimental work with the elements, the reactions of the various parts of the eye assume an important role. If, in the natural course of events, supersonic speed becomes a common adjunct of civilization, its effect on man must be known. It has been determined by Duguet and Mercier[8] that loss of goggle protection results in irreversible changes from frostbite in the cornea; the cornea is extremely vulnerable, owing to its avascularity and to its rapid loss of the protective lacrimal film through evaporation. Tagawa[9] determined corneal changes in the rabbit when very low temperatures were applied; analogous findings were obtained. He found that edematous degenerative changes of the corneal tissues resulted, accompanied by an infiltration with leucocytes.

Maintenance of corneal transparency is of paramount importance. Edema, the first reaction to insult, reduces this transparency, with a resultant loss of vision. Maximum transparency is obtained when the amount of water is 200 to 400% of the weight of the dry matter; this corresponds to the physiologic water content of fresh corneas.[10] Various solutions were tried, and loss of the mucoid (mucopolysaccharide) was always followed by clouding of the cornea. The greatest amount

5. Zander, E., and Weddell, G.: Observations on the Innervation of the Cornea, J. Anat. **85**:68, 1951.

6. Spadavecchia, V.: Nervous Regulation of the Cornea, Ann. ottal. e clin. ocul. **77**:353, 1951.

7. Cogan, D. G., and Ginsberg, J.: Representation of Corneal and Conjunctival Sensation in the Central Nervous System, A. M. A. Arch. Ophth. **47**:273, 1952.

8. Duguet, J., and Mercier, A.: Ophthalmologic Problems of Supersonic Speed and Flight in the Stratosphere, Ann. ocul. **184**:969, 1951.

9. Tagawa, S.: Influence of Low Temperatures on Ocular Tissues, Acta Soc. ophth. jap. **56**:14, 1952.

10. van Walbeek, K., and Neumann, H.: Studies of Corneal Transparency Under Various Experimental Conditions, A. M. A. Arch. Ophth. **46**:482, 1951.

of swelling was always found after application of water. Maurice and Giardini [11] added to this work by determining the effect of removal of the limiting membranes of the cornea. They noted that loss of the epithelium was followed by a rapid increase (0.5% per minute) in thickness, varying considerably in different animals, however. The greatest amount of swelling was always found in the center of the cornea. Usually the maximum (200%) was reached in 24 hours; a decrease in swelling was seen after 2½ days, the normal state being reached 1 to 4 days later. Loss of endothelium resulted in a much more rapid increase in thickness (2% per minute, 100% in 1 hour, and 500% in 24 hours). The removal of Descemet's membrane was followed by a rate of swelling of 3% per minute.

According to Cogan,[12] the transparency of the cornea is chiefly due to a state of deturgescence, which maintains the necessary quantitative and qualitative fluid balance throughout its structure. The deturgescence is the result of the constant osmosis, which withdraws fluid from the anterior and posterior surfaces. When cloudiness is present, it is due to reflections from multiple interfaces of substances of one refractive index suspended in a medium of a different refractive index. The avascularity of the cornea is maintained primarily through the above-described normal state of deturgescence and absence of swelling. When edema supersedes, therefore, neovascularization takes place. Limbal resistance and stromal compactness prevent distortion of all but the posterior surface. Making up the cornea, histochemically, are collagen and a specific mucopolysaccharide; water is absorbed rapidly by the former.

If Cogan is correct in believing that the loss of fluid is due to osmotic forces, one must assume that the endothelium is impermeable to chloride ions, a conclusion which is not supported by the findings of Maurice. The latter believes that there is an active transfer of some ion, possibly sodium, across the endothelium of the cornea to the aqueous humor. If the cornea is permeable to sodium, it is permeable also to chloride. Furthermore, simple excretion of water from the cornea is possible, but not probable, in view of the fact that the process would be the least efficient energetically of all the methods of keeping the cornea in a relatively dehydrated state. Part of the energy required for the transfer of water out of the cornea comes from the cornea itself, as well as from evaporation of tears and the secretory activity of the ciliary body.

The rate and mechanism of wound healing [13] are of great significance, both medically and industrially. Particularly important is the effect of cortisone, since that drug has been so widely adopted by the clinical ophthalmologist. Von Sallmann and associates [14] have contributed to our knowledge on this score; from their work on rats, they concluded that cortisone applied after superficial trauma caused slight inhibition of corneal reepithelization. In the same way, the formation of granulation

11. Maurice, D. M., and Giardini, A. A.: Swelling of the Cornea in Vivo After the Destruction of Its Limiting Layers, Brit. J. Ophth. **35**:791, 1951.

12. Cogan, D. G.: Applied Anatomy and Physiology of the Cornea, Tr. Am. Acad. Ophth. **55**:329, 1951.

13. Maurice, D. M.: Permeability to Sodium Ions of the Living Rabbit's Cornea, J. Physiol. **112**:367, 1951.

14. von Sallmann, L.; Jones, I. S.; Wiggins, R., and Locke, B. D.: Influence of Cortisone on Wound Healing, Macrophagocytosis, and Capillary Permeability, Wien. klin. Wchnschr. **63**:684, 1951.

tissue is inhibited in the monkey's sclera after trephining, and healing takes place by dense scar formation. Therefore one infers that healing is somewhat hindered, rather than helped, by the local use of cortisone. Ashton and Cook [15] also attempted to show whether or not cortisone was beneficial in promoting healing. They found from their studies on rabbits that the effect of cortisone on the healing process of the cornea is the inhibition of the formation of a fibrinous coagulum, of cellular infiltration, of fibroblastic repair, and of regeneration of the epithelium. The findings are almost directly proportional to the amount of cortisone administered.

By use of the slit lamp, Linnén [16] was able to observe the mechanism of closure of corneal wounds; observations were made after trephining of the eyes of guinea pigs. He made central trephine openings of 1 mm. diameter in the cornea to determine whether the healing was due to processes in the epithelium, to keratoblast formation, to active interstitial formation of fixed corneal cells, to participation of the endothelium, or to other factors. After a large perforating injury of the cornea, such as that following trephine, there are three stages in the process of healing, which are described by Linnén:

1. With the exit of the aqueous, the lens and iris come forward; the corneal concavity lessens; the trephine opening becomes constricted ovally in the area of the endothelium, and fibrin begins to form just posterior to the corneal opening.

2. The anterior chamber begins to re-form slightly; the iris is still pushed forward. The cornea resumes its convex form; thus the trephine opening is reversed in position, and the fibrin plug is caught in the opening, thus closing the opening.

3. The anterior chamber is re-formed, with traction visible in the cornea on its convex curvature.

Thus, he shows that healing is a complex process, with several of the ocular components participating.

Cogan [12] believes that epithelial healing is primarily dependent upon regeneration or mitosis, which occurs only in the two posterior layers. A single-cell mitotic cycle lasts approximately 70 minutes; the resting stage lasts 1 week, and about 5,000 to 6,000 cells are normally in mitosis at any one time. In contradiction, Grawitz [17] declares that the epithelial cells of the cornea are transformed into leucocyte-like cells; these do not migrate from any other part of the eye. In all cases, infectious and otherwise, in which he made tests, the leucocyte-like cells were transformed epithelial cells. On the other hand, Friedenwald [18] is of the opinion that the newly formed corneal epithelium is the result of metaplasia of the ingrowing conjunctival epithelium. In his experiments on rabbits he showed that after the epithelium was scraped off the cornea of each eye, new epithelium grew in from the limbus, completely covering the denuded area in five to seven days.

DIAGNOSIS AND THERAPY

Classification of disease subserves a didactic rather than a clinical function. However, it is always practical to contribute to the adoption of a system which is

15. Ashton, N., and Cook, C.: Effect of Cortisone on Healing of Corneal Wounds, Brit. J. Ophth. **35**:708, 1951.

16. Linnén, H. J.: Slit Lamp Observations on Closure Mechanism of Corneal Wounds After Trephine on Guinea Pig Eyes, Klin. Monatsbl. Augenh. **117**:606, 1950.

17. Grawitz, P. B.: Transformation of the Corneal Epithelium into Cells Resembling Leukocytes, von Graefes Arch. Ophth. **152**:314, 1951.

18. Friedenwald, J. S.: Growth Pressure and Metaplasia of Conjunctival and Corneal Epithelium, Docum. Ophth. **5-6**:184, 1951.

simple, as well as universal. Dunphy [19] presents a classification of the various diseases of the cornea in seven categories. However, he feels that this tabulation is only a temporary measure, one which will be both modified and improved with increasing knowledge of etiologic factors and basic mechanisms. A similar attempt is offered by Busacca,[20] who classifies corneal pathology according to the three layers affected: (1) epithelial-parenchymatous layer (the epithelium, Bowman's membrane, and the superficial layers of the parenchyma); (2) parenchyma, and (3) endothelial-parenchymatous layer (deepest layers of the parenchyma, Descemet's membrane, and the endothelium). He further describes in detail the following: (*a*) elementary lesions due to retrogressive changes; (*b*) types of corneal haze, especially the inflammatory types, which he separated into white and gray. From these references can be seen the welter of confusing ideas and names associated with corneal pathology. It is almost a truism that for every country there is at least one different method of classification, as well as names.

Spadavecchia [21] tried to limit his classification to those corneal lesions which were neurogenic. He states that, clinically, one encounters punctate, miliary, disciform, ring-like, nummular, band-like, nodular, central or paracentral, peripheral, and diffuse types of lesions. He tried to include these types in the groups formed on the basis of the type of change undergone by the cornea to form such lesions; these changes may be infiltrative, edematous, vesicular, dystrophic, dendritic, sclerosing, filamentous, striate, plexiform, or reticular. This, however, does not contribute any more than any of the other classifications to the simplicity of the system, to efficiency, or to the increased knowledge of the ophthalmologist.

Vascularization.—Vascularization of the cornea continues to be a crippling complication of corneal affections. It is also a possible consequence of surgical procedures on the cornea. Vascularization can be produced by phlyctenular disease, interstitial keratitis, sclerosing keratitis, disciform keratitis, rosacea, various ulcers, mechanical irritation, nutritional disturbance, and several dystrophies, among others. It is necessary to determine the location and depth of the vessels in order to make the differential diagnosis. Early in the disease the vessels are of some benefit for the nutrition of the cornea, but the persistence and progressive increase of the vessels damage the cornea, with consequent loss of vision.[22]

Experimental work submitted by Bessière and Teulières [23] to determine the site of vascularization following various types of injuries indicated that vascularization is a constant consequence of irritation near the limbus. This was true also of implants; when their distance from the limbus was 3 mm. or less, vessels were always found. These authors do not agree with the Cogan theory that corneal edema is the fore-

19. Dunphy, E. B.: Classification of Diseases of the Cornea, Tr. Am. Acad. Ophth. **55**:382, 1951.

20. Busacca, A.: An Attempt to Classify Elementary Corneal Lesions, Bull. et mém. Soc. franç. opht. **64**:281, 1951.

21. Spadavecchia, V.: Systematization of Neurogenic Corneal Affections, Boll. ocul. **30**:611, 1951.

22. Doggart, J. H.: Vascularization of the Cornea, Brit. J. Ophth. **35**:160, 1951.

23. Bessière, E., and Teulières, J.: Note on Experimental Vascularization of the Cornea, Arch. opht. **11**:268, 1951.

runner of new-vessel formation. They lean toward the belief that the toxins produced by tissue damage provide the stimulus.

Cortisone is conceded to be the drug of choice to combat vascularization. It has been found to be effective both against the vessels already formed and against the formation of new vessels. In one subject, it was found that 1.25 mg. of cortisone acetate injected subconjunctivally reduced the extent of a vascular area by about 45% and the rate of longitudinal capillary growth by about 30%. The amount of reduction by the cortisone is increased when the distance of the vascularization from the limbus is greater. Effectivity is produced either by daily doses or by doses given every three to four days. Subconjunctival injection is the method of choice.

Herpetic Keratitis.—The universal and most effective method of treating herpetic keratitis at present is with aureomycin, administered in the form of a solution, ointment, or capsule. In most cases reported favorable results are obtained. A few authors report no beneficial effects, but these are not many. Aureomycin shortens, and even arrests, the course of the disease and is efficacious in preventing the well-known complications of herpetic lesions of the cornea.

Cortisone and corticotropin have also been tried as therapeutic measures in this disease. However, it has been found by several groups of workers [24] that the course of the disease was not favorably influenced by the use of cortisone or corticotropin. This was true with all routes of administration. Large doses caused a prolongation of the infection, and even acute exacerbations of the lesions.

A few other methods have been tried, and I shall mention them in passing. Kronenberg [25] advocates the use of an ether swab, with which he removes the epithelium. Silvan [26] suggests hormonal therapy, such as the use of progesterone. Methenamine (urotropin®) and urea were also recommended. Very few patients have been so treated.

Phlyctenular Keratoconjunctivitis.—Phlyctenular keratoconjunctivitis is a disease which has been known for years; the etiologic considerations have been legion. For many years it was believed that the causative disease was tuberculosis. This belief lost favor in the 30's and has again become popular. The arguments in favor of this origin derive chiefly from the work of Thygeson [27]; he has proved that the phlyctenule is essentially an allergic manifestation of primary tuberculosis, occurring predominantly in childhood. It is an allergic reaction to the bacterial proteins of the tubercle bacillus. His belief is based on the following factors:

1. The high incidence of positive tuberculin reactions.
2. The high incidence of radiographically demonstrable tuberculous chest lesions.
3. The high incidence of a history of past or present tuberculosis.
4. The high incidence of family history of tuberculosis.

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24. Ormsby, H. J.; Dempster, G., and van Rooyen, C.: Effect of Cortisone on Experimentally Induced Herpetic Keratitis of the Rabbit, Am. J. Ophth. **34**:1687, 1951. Hallett, J.; Leopold, I., and Steinmetz, C.: Effect of Systemic Cortisone and Corticotrophin (ACTH) on Experimental Herpes Simplex Keratitis, A. M. A. Arch. Ophth. **46**:268, 1951.

25. Kronenberg, B.: Further Report on Use of Ether in the Treatment of Herpetic Keratitis, New York J. Med. **50**:2825, 1950.

26. Silvan, F.: Recurrent Postmenstrual Herpetic Keratitis: Report of a Case, Arch. Soc. oftal. hispano-am. **11**:168, 1951.

27. Thygeson, P.: The Etiology and Treatment of Phlyctenular Keratoconjunctivitis, Am. J. Ophth. **34**:1217, 1951.

5. The high incidence of subsequent clinical tuberculosis.

6. The clinical similarity of phlyctenular ophthalmia to the complications of the ophthalmoreaction of Calmette in tuberculous patients.

7. The significant incidence of previous phlyctenulosis in adults suffering from tuberculosis.

8. The worldwide parallelism between the incidence of tuberculosis and the incidence of phlyctenulosis.

9. The rapid disappearance of the phlyctenule under anti-allergic therapy known to be capable of abolishing the tuberculin reaction, notably cortisone therapy.

Fujii,[28] in examining cytologically the material expressed from phlyctenules, found that epithelioid cells and giant cells were oftenest present. This observation is in agreement with Thygeson in assigning the etiologic role to tuberculosis, since these findings closely resemble the cytologic structure of tubercles.

Up to the present time therapy has been mainly symptomatic and general, rather than specific. In some cases tuberculin desensitization has been tried, but the results are still too unpredictable for general acceptance. Dietary therapy is a valuable adjunct to the active treatment of phlyctenular keratoconjunctivitis but should not be the sole method of attack. It is a well-known fact that improved environmental and nutritional conditions cause a decreased incidence and susceptibility to infectious disease and thus would also be helpful in reducing the incidence of tuberculosis and phlyctenulosis.

Topical antiseptics are of no particular value against phlyctenular keratoconjunctivitis. In the past several years cortisone has given extremely favorable, and, indeed, very rapid, results when used in cases of phlyctenular keratoconjunctivitis. Many workers[29] have found a rapid disappearance of the lesions within 24 to 48 hours. When lesions reappeared after cessation of therapy, they responded rapidly to a second course of cortisone.

Ocular Tuberculosis.—Tuberculosis of the eye, as a distinct entity, is no longer as common a disease as it was in former years. Keratitis can still be found as a complication of the systemic infection, however. Newer and better methods of therapy are now available to combat this. British workers[30] advocate the use of paraaminosalicylic acid combined with streptomycin. Their results showed marked improvement, although it was short-lived, for the improvement was not prolonged after cessation of therapy. Diener[31] suggests using large doses of vitamin D_2 because of the successful use of this vitamin in skin tuberculosis. Calciferol (vigantol®), 10 mg. of vitamin D_2, was given perorally every other day until 24 ampules in all had been given, then 1 ampule biweekly, and, finally, 1 ampule a week for several months. He reports good results. A new drug, used first by

28. Fujii, S.: Cytological Study of Phlyctenular Keratoconjunctivitis, Acta Soc. ophth. jap. **56**:30, 1952.

29. Barios, P., and Vasquez Barrière, R.: Cortisone in Ophthalmology, Arch. Soc. oftal. hispano-am. **11**:276, 1951. García Nocito, P. F.: Ocular Diseases and Cortisone, Semana méd. **99**:531, 1951. Fine, M., and Goodwin, R.: Evaluation of Local Cortisone Therapy in Ophthalmology, A. M. A. Arch. Ophth. **47**:787, 1952.

30. Horne, N., and Macaskill, J.: Effect of Para-Aminosalicylic Acid Alone and in Association with Streptomycin on Experimental Ocular Tuberculosis, Brit. J. Ophth. **35**:459, 1951.

31. Diener, F.: Treatment of Ocular Tuberculosis with Large Doses of Vitamin D_2, Klin. Monatsbl. Augenh. **119**:528, 1951.

Gandolfi and Morpurgo [32] in this respect, is thiosemicarbazone; a favorable response is reported in three cases of keratitis.

Burns of the Cornea.—Burns of the cornea are found with increasing frequency as a result of occupational hazards. Efficient methods of therapy are therefore of great importance. The use of sulfhydryl (known as "hydrosulphosol") for this lesion has recently been reported by Cruthirds [33]; he found that the drug prevents infection and stimulates prompt healing in cases of chemical and thermal burns of the eye. This, of course, presupposes rapid treatment within the first 24 to 48 hours. Even roentgen burns have responded to this therapy. Preservation of most, if not all, of the vision is noted. Nagy [34] has used the vasodilator benzazoline (priscol®), with great success. He instilled a 10% aqueous solution three to five times daily, with satisfactory results. His work does not have the support of numerous cases, however, as does that of Cruthirds.

Syphilitic Keratitis.—Interstitial keratitis as caused by congenital syphilis is still a common enough disease of the cornea to be mentioned here, albeit briefly. In the words of Riehm,[35] it has long been considered an allergic process, for the following reasons:

1. First one eye is affected, and regularly, after weeks or months, the second eye becomes involved.
2. An eye can have typical primary keratitis only once.
3. The histologic picture speaks against a true syphilitic infection of the cornea.
4. The course of the ocular disease is unaffected by antisyphilitic treatment.
5. Such treatment cannot prevent development of keratitis in the second eye.
6. The cornea of the newborn may contain large numbers of spirochetes and yet be perfectly clear and transparent.

This author believes that the degeneration of the spirochetes in the cornea releases endoallergic substances, by means of which an allergic keratitis is engendered. Since the chief complication of interstitial keratitis is deep vascularization, with consequent loss of vision, it is not surprising to find that cortisone has been used actively in the therapy of this affection, in view of the previously mentioned beneficial effects of this substance on neovascularization elsewhere in the cornea. Geddes and McCall [36] gave cortisone over a period of four weeks; the initial dose was 100 mg., with 200 mg. on the second, third, and fourth days. A daily maintenance dose of 100 mg. was then given. Six days after institution of treatment, the right eye was 70% clear, and the disease had been arrested in the left eye. At the end of 28 days only a few of the deep vessels were still visible with the slit lamp. Horne [37] found the same good results with topical use of cortisone, even

32. Gandolfi, C., and Morpurgo, F.: Thiosemicarbazone (TB1-698) in Treatment of Ocular Tuberculosis, Arch. ottal. **55**:293, 1951.

33. Cruthirds, A.: Sulfhydryl in Tissue Respiration and Repair as Applied to Burns in Ophthalmology, J. Internat. Coll. Surgeons **16**:356, 1951.

34. Nagy, F.: Treatment of Burns of the Eye, Ophthalmologica **121**:345, 1951.

35. Riehm, W.: Pathogenesis of Parenchymatous Keratitis in Its Relation to Allergy, Klin. Monatsbl. Augenh. **120**:50, 1952.

36. Geddes, A., and McCall, M.: Interstitial Keratitis Treated with Cortisone, Canad. M. A. J. **63**:601, 1950.

37. Horne, G.: Topical Cortisone in Treatment of Syphilitic Ocular Disease, Brit. M. J. **1**:1289, 1951.

with doses as small as one drop of a solution containing 5 mg. per cubic centimeter of isotonic sodium chloride solution instilled every three hours. Contradictory findings were reported by Maddin and Danto [38]; topical application of cortisone was used, with unsatisfactory results. However, this may have been because treatment was not instituted until some time after the onset of the disease—in one case seven months.

Other Types of Keratitis.—A few sentences will suffice here to recall other, rarer types of keratitis. One must always keep in mind the possibility of contamination with Pseudomonas aeruginosa. The treatment of choice is streptomycin, administered either topically or subconjunctivally. The severe keratitis following the lagophthalmos of leprous polyneuritis has been treated with diaminodiphenylsulfone, with failure; some benefit has resulted from use of the tissue therapy of Filatov. The keratitis of mycosis fungoides is a rarity but can be very severe. Keratoplasty is recommended. The papers presented on dystrophic lesions of the cornea are primarily of academic interest, since there is little, or no, active treatment which can be said to be successful except in the case of keratoconus, which will be mentioned again later.

Additional Forms of Therapy.—1. Antibiotics: Aureomycin has been found to be successful in the therapy of viral lesions of the cornea, as previously indicated. It can be used as a 0.5% suspension in castor oil or as an aqueous solution.

Oxytetracycline ("terramycin") hydrochloride was found to be more stable in solution than is aureomycin. This drug has been shown to be very effective against the alpha hemolytic Streptococcus. Few, if any, toxic side-effects are noted.[39] It is usually applied topically as a solution every two hours.

Chloramphenicol (chloromycetin®), one of the latest antibiotics to be introduced, is easily prepared, stable, nonirritating, and nontoxic. It is considered effective against a wide range of bacterial infections.[40]

Neomycin is still more or less in the experimental stage, but it has been shown that in a concentration up to 40 mg. per cubic centimeter, or 5,000 units per cubic centimeter, there is no interference with epithelial regeneration.[41] Higher concentrations may result in damage to the corneal endothelium, as well as to other ocular structures. It is beneficial, however, in the therapy of bacterial keratitis.

Oidiomycin 101, an extract from oidium lactis, is another new drug. It is said to be of some therapeutic aid in a few selected cases of keratitis, but reports in the literature are still lacking.

2. Cortisone and Corticotropin: A few further comments on the use of cortisone in ophthalmology are indicated here. So many ocular diseases respond to it that dosages and effects should be discussed, at least to a slight extent. In addition to those lesions already mentioned, small marginal corneal lesions or ulcers, lime burns of the cornea, superficial keratitis, nonsyphilitic deep keratitis, disciform keratitis,

38. Maddin, S., and Danto, J.: Results of Topical Application of Cortisone in Congenital Syphilitic Interstitial Keratitis: Preliminary Report of 2 Cases, A. M. A. Arch. Dermat. & Syph. **64**:437, 1951.

39. Douvas, N.; Featherstone, R., and Braley, A.: Role of Terramycin in Ophthalmology, A. M. A. Arch. Ophth. **46**:57, 1951.

40. Roberts, W.: Topical Use of Chloramphenicol in External Ocular Infections, Am. J. Ophth. **34**:1081, 1951.

41. Vogel, A.; Leopold, I., and Nichols, A.: Neomycin, Am. J. Ophth. **34**:1357, 1951.

metaherpetic ulcer, and bullous keratitis show improvement after therapy with cortisone. The most dramatic effects are seen when the tissue reaction is still largely vascular and lymphatic in nature. There are various means of using cortisone; when used topically, it is given as drops in a 1 : 3 or 1 : 4 dilution, every one to four hours daily. Subconjunctivally, it is given in doses of 0.2 to 0.5 cc. one to two times a week. It can also be given intramuscularly as a daily dose of 100 mg. and intravenously in a 5% dextrose solution drip.[42]

Not all the effects are good. During wound healing, there are inhibition of the formation of a fibrinoid coagulum and retardation of the formation of granulation tissue and of cellular infiltration. Fibroblastic activity is also retarded. There are also definite metabolic side-effects from the use of cortisone and corticotropin; these are an impairment of carbohydrate tolerance, which induces glycosuria or upsets existing diabetes; alteration in protein metabolism; increased mobilization and utilization of fats; disturbance in distribution of electrolytes and water; lysis of fixed lymphatic tissue; complementary effects on the other endocrine organs, and mental disturbances. Systemic administration is contraindicated in cases of diabetes, hypertension, chronic nephritis, and psychotic states.

SCLERA

The sclera usually finds meager representation in the literature. The past year has been no exception. However, there is mention of progressive scleroperikeratitis.[43] This lesion has also been known as annular scleritis. There is a progressive, painful, brawny inflammation of the eyeball, which leads to blindness and necessity of enucleation. The cornea and sclera show round-cell infiltration, with many eosinophiles and follicular formation. The cause is still undetermined, and no means of arresting the disease has yet been found.

Various other lesions may affect the sclera. Nodules are found fairly frequently in persons past 50 years of age; the origin is very often rheumatoid arthritis. The nodules can be of a slowly progressive inflammatory type, as described above, or of a nonprogressive, noninflammatory type. Perforating lesions also may occur as a complication of a systemic disease.[44]

To date, cortisone is the single, most effective means of treating the various diseases which affect the sclera. There is a definite regression of the nodules histologically after therapy with cortisone. Nonspecific scleritis and episcleritis also show marked improvement after use of cortisone.[45]

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42. Agatston, H.: Use of Cortisone in Ocular Conditions, Am. J. Ophth. **34**:1655, 1951. Brückner, R.: Experiences with Cortisone Applied Locally, Ophthalmologica **121**:275, 1951. Woods, A.: Present Status of ACTH and Cortisone in Clinical Ophthalmology, Am. J. Ophth. **34**:945, 1951.

43. Leibiger, W.: Progressive Scleroperikeratitis: Report of a Cases, Klin. Monatsbl. Augenh. **119**:629, 1951. Voss, H.; Progressive Scleroperikeratitis, with Late Involvement of the Orbit, von Graefes Arch. Ophth. **151**:116, 1951.

44. Malbrán, J., and Manzitti, E.: Scleromalacia and Conditions Which It Resembles, Ann. ocul. **184**:679, 1951.

45. Moutinho, H., and Basto, L.: Ocular Therapy with Cortisone Applied Locally, Arch. opht. **11**:241, 1951.

SURGICAL METHODS

Keratoplasty is still receiving most attention in the field of corneal surgery. Until the past few years, patients with keratoconus had to suffer from loss of vision, without any redeeming hope. Now, among other methods, keratoplasty offers some help to these persons.[46] Legrand [47] discusses both medical and surgical therapy; he favors keratoplasty as the treatment of choice and recommends the Sato approach. He, further, is of the opinion that the former method of iridectomy is almost valueless except in the case in which more extensive surgery is contraindicated by other factors.

Straub [48] sets forth a more complete description of Sato's operative treatment of keratoconus. He regards the spontaneous tears in Descemet's membrane as a kind of self-healing. According to Sato's method, the apex of the keratoconus is flattened and stabilized by scarring of the substantia propria. The direction of the folds in the substantia propria (the lines seen with the slit lamp) corresponds to the lines of greatest tension and greatest resistance, with the opposition of progressive distention. When the incision is made parallel to the conus lines, good results are obtained. The keratoconus knife of Sato is used to insure against the loss of aqueous. The keratoplasty follows this procedure.

There are two schools of thought as to the type of keratoplasty to be used when surgery is indicated. Poyales [49] and Paufique,[50] among others, seem to approve the partial penetrating type. In his discussion of this operation, Poyales states that the patients should be given penicillin and streptomycin before operation and that the donor material should be used very shortly after the death of the donor. He uses a round graft and constricts the patient's pupil with physostigmine before the operation. Border-to-border sutures hold the graft in place and are removed with the onset of ciliary irritation (10th to 15th day). Retrobulbar anesthesia after operation eliminates the axon reflexes arising from the many corneal sutures.

Castroviejo,[51] on the other hand, favors total penetrating keratoplasty when the cornea has been affected by a dystrophic disease. Prolapse of vitreous is always an accompaniment but can be minimized by complete relaxation of the extraocular muscles and reduction of pressure on the eye at the time of operation. Of 21 eyes on which he operated, 13 remained clear or, at the most, slightly nebulous. The other eyes showed clouding or opacification of the graft to an extent that vision was not at all improved. This method, total penetrating keratoplasty, is offered as a possible means of improving vision in eyes which heretofore have been considered unfavorable for surgical intervention.

Keratoplasty is not a procedure which should be undertaken lightly. It is indicated in the following conditions: epithelioma, symblepharon, dystrophies of the

46. Amsler, M.: Keratoconus, Bull. et mém. Soc. franç. opht. **64**:272, 1951. Roschin, V.: Histopathology of Keratoconus, Vestnik oftal. **30**:25, 1951.

47. Legrand, J.: Treatment of Keratoconus, Année thérap. en ophtal. **2**:206, 1951.

48. Straub, W.: Operative Treatment of Keratoconus After Sato, von Graefes Arch. Ophth. **151**:701, 1951.

49. Poyales, A.: Partial Penetrating Keratoplasty, Arch. Soc. oftal. hispano-am. **11**:746, 1951.

50. Paufique, L.: A Few Improvements in Keratoplasty, Bull. et mém. Soc. franç. opht. **64**:252, 1951.

51. Castroviejo, R.: Total Penetrating Keratoplasty, Am. J. Ophth. **34**:1697, 1951.

cornea, keratoconus, interstitial keratitis, and deep corneal ulcers when there is no possible way to improve the vision by other means. Lamellar keratoplasty is, of course, a much safer procedure. The age, the condition of the cornea, the state of the patient, and last, but not least, the prognosis must all be considered before surgical intervention is advised.

Several new thoughts concerning keratoplasty have recently appeared. Paufique [50] suggests that the iridosclerectomy done at the end of the operation be eliminated, since secondary glaucoma following keratoplasty is unusual. He further recommends that if the graft becomes somewhat opaque within the first fortnight it should be changed at once. Direct sutures are superior to those formerly used. He employs cortisone after the first week if any reaction is present. For vessels which form in the graft, beta-irradiation is very useful.

There are many complications which appear to imperil the graft. Quite often there is a violent ciliary reaction, produced by the heteroproteins of the graft when it had not been conserved on ice long enough. In addition to this, there are hypertension, controlled by paracentesis in purely corneal lesions and more difficult to control in eyes with deeper pathologic processes; a delayed anterior chamber possibly due to faulty fitting of the graft, corrected by placement of additional sutures, or perhaps caused by the penetration of a suture into the anterior chamber, corrected by removal of the suture; prolapse of the iris, which must be excised or the synechia separated, and late opacification of the graft, which is the most serious of the complications. This appears about three months after the operation and eventually involves all the layers of the cornea. It has been suggested that the recipient should be desensitized by serum from the donor before the keratoplasty, but in almost all cases this is not a feasible procedure. Cortisone and corticotropin have also been suggested in this capacity.[52] The possibility of transmitting latent syphilis by means of a graft was also considered. This possible complication was disproved by Randolph.[53]

Several other types of corneal surgery have been reported. Worcester [54] suggests using a corneal cap in corneal transplantation; he found that the cap was well tolerated and prevented untoward reactions in most cases. Sclera was tranplanted into the cornea by Winkelman [55]; the dehydrated sclera showed some transparency and in the graft was almost as transparent as the cornea. Plasma implantations were also tried; the host cornea was able to build up into this plasma medium a new tissue closely resembling normal cornea in its histologic structure and transparency, except for a slight central clouding of Descemet's membrane.[56] This procedure has only theoretical value at this time.

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52. Mueller, H., and Maumenee, A.: Diseases of the Corneal Graft, Arch. opht. **11**:146, 1951.

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55. Winkelman, J.: Optical Behavior of Sclera Transplanted into Cornea, Am. J. Ophth. **34**:1379, 1951.

56. van Alphen, G. W. H. M.: Plasma Implantations in the Cornea, Am. J. Ophth. **35**:701, 1952.

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News and Comment

EDITED BY DR. W. L. BENEDICT

GENERAL NEWS

National Council to Combat Blindness, Inc.—Applications for the 1953-1954 grant-in-aid awards of the National Council to Combat Blindness, Inc., will be considered by the organization's Committee on Research at its fourth annual meeting, to be held in the spring of 1953. Completed applications should be received in the office of the Council no later than April 15, 1953. Forms may be obtained by addressing the secretary, National Council to Combat Blindness, Inc., 1186 Broadway, New York 1.

The Council, in accordance with its research program, encourages applications for grants to projects encompassing the scientific principles that are related to the study of sight, both normal and pathological, including the various branches of biological, chemical, and physical science, and clinical investigative medicine.

Serving on the Committee on Research are Phillips Thygeson, M.D., Professor of Ophthalmology, University of California School of Medicine, San Francisco; James H. Allen, M.D., Professor of Ophthalmology, Tulane University of Louisiana School of Medicine, New Orleans; Alson E. Braley, M.D., Director, Department of Ophthalmology, University Hospitals, State University of Iowa College of Medicine, Iowa City; Dan M. Gordon, M.D., Assistant Professor of Clinical Surgery, Department of Ophthalmology, New York Hospital—Cornell Medical Center, New York; Charles Haig, Ph.D., Department of Physiology and Pharmacology, New York Medical College, Flower and Fifth Avenue Hospitals, New York; Stuart Mudd, M.D., Professor of Bacteriology, University of Pennsylvania, Philadelphia; Charles A. Perara, M.D., Assistant Clinical Professor of Ophthalmology, Columbia University College of Physicians and Surgeons, New York, and Samuel L. Saltzman, M.D., Assistant Clinical Professor of Ophthalmology, New York Medical College, Flower and Fifth Avenue Hospitals, New York.

Grants-in-aid approved by the Committee for the period 1952-1953 are as follows: (Continuation) Retina Foundation, Massachusetts Eye and Ear Infirmary, Endre A. Balzs, M.D., $2,500, Acid Mucopolysaccharides in the Vitreous Body; (continuation) University Hospitals, State University of Iowa, Herman M. Burian, M.D., $5,000, Study of the Electrical Response of Retina and Brain in Patients with Amblyopia ex Anopsia and Suppression; New York Eye and Ear Infirmary, Bernard Goldberg, M.D., and Bernard Levine, M.D., $2,500, Possible Role of Hyperestrinism in the Etiology of Retrolental Fibroplasia; Wills Eye Hospital, Philadelphia, Harry Green, Ph.D., and Irving H. Leopold, M.D., $3,750, Investigation of the Intermediary Reactions and the Enzyme Systems Involved in the Anaerobic Glycosis by the Lens; New York Medical College, Flower and Fifth Avenue Hospitals, Charles Haig, Ph.D., $2,625, Detection of Plane-Polarized Light by the Human Eye; Stanford University, San Francisco, Arthur Jampolsky, M.D., $2,500, Visual Characteristics of Macular and Poripheral Retina in Amblyopia Associated with Convergent and Divergent Deviation; University of Louisville, School of Medicine, Arthur H. Keeney, M.D., $2,445, Role of Estrogenic and Androgenic Substances on the Retinal Vascular Pattern in Alloxan-Diabetic Rats; Yale University School of Medicine, J. Alexander Van Houven, M.D., $560, Treatment of Artificial Corneal Burns with Various Substances Related to Adrenaline and Its Derivates; Indiana University Medical Center, Fred M. Wilson, M.D., $1,596, Norms and Techniques of Corneal Biostandardizations of Beta-Irradiation Applicators for Use in Ophthalmology.

Basic Course in Orthoptics for Technicians Sponsored by American Orthoptic Council.—The basic course in orthoptics sponsored by the American Orthoptic Council will be given in 1953 in the Department of Ophthalmology, State University of Iowa College of Medicine, Iowa City. The course will consist of didactic lectures and practical demonstrations, given by outstanding teachers. It will be held from June 15, 1953, through Aug. 15, 1953.

High school graduates are eligible to take this course, but preference will be given to applicants with at least two years of college training, or its equivalent.

The tuition is $150, of which $50 is payable on application, the remaining $100 to be paid at the time of registration. Arrangements have been made for the participants to be housed in the nurses' home and to have their board at the University Hospitals. The cost for room, board, and laundry will be approximately $75 per month per person.

In order to be eligible to take the examination leading to certification by the American Orthoptic Council, a candidate must have, in addition to the basic course sponsored by the Council, or an equivalent course, a minimum of seven months of practical training under a certified orthoptic technician in an office or institution approved by the Council. The Council makes every effort to find suitable positions for training for all participants in the course who desire one.

Those wishing to obtain further information about the course or to apply for admission should write to Hermann M. Burian, M.D., Chairman, Committee on Instruction, University Hospitals, Iowa City.

Books

Ophthalmic Pathology: An Atlas and Textbook. By Jonas S. Friedenwald, M.D.; Helenor Campbell Wilder; A. Edward Maumenee, M.D.; T. E. Sanders, M.D.; Michael J. Hogan, M.D.; W. C. Owens, M.D., and Ella U. Owens, M.D. Published under the joint sponsorship of the American Academy of Ophthalmology and Otolaryngology and the Armed Forces Institute of Pathology. Price, $18. Pp. 489, with 240 plates. W. B. Saunders Company, 218 W. Washington Sq., Philadelphia 5, 1952.

This entirely new textbook and atlas of ophthalmic pathology represents the combined efforts of the American Academy of Ophthalmology and the Armed Forces Institute of Pathology to present to the student and practitioner of ophthalmology a comprehensive text (fulfilling the requirements of each in the field) of ophthalmic pathology. It is an outgrowth of the "Atlas of Pathology" by DeCoursey and others, first published by the Academy in 1938. The format has been changed to include a text, based on J. S. Friedenwald's "Pathology of the Eye," and illustrations have been used to amplify the text, rather than a presentation of isolated case reports, as in the original atlas.

Although not primarily designed as a reference book, the volume will nevertheless be valuable to the reader as such because of the comprehensive bibliography included. The very large collection of material in the Registry of Ophthalmic Pathology has been freely drawn upon for the very excellent photomicrographs used to illustrate the text.

Emphasis has been placed throughout on physiologic mechanisms and their aberrations resulting in pathologic changes in the eye. The idea that ocular pathology is but an extension of general pathology, applied to a somewhat specialized organ, is stressed. Normal physiologic and anatomical principles are considered in introductory chapters, and reiterated or enlarged upon in later chapters wherever necessary to aid in the understanding of specific pathologic processes.

An outstanding feature is a chapter on the nature and mechanism of inflammation. This is a detailed description of the present concepts of the cytology and chemistry of inflammatory and immune processes. The discussion has been simplified enough to be readily understood by the average reader; yet all sides of controversial questions have been included and fairly treated. Those portions of the chapter dealing with the intricacies of the various types of hypersensitivity reactions will be especially valuable to the resident and the practitioner alike.

The remainder of the book is devoted to a consideration of the pathology of the eye itself. Its general organization is such that the emphasis is placed on disease entities, rather than on the specific portion of the eye involved. More than ordinary consideration is given to correlation of clinical and pathologic findings. Wherever possible, an attempt has been made to substitute simple descriptive and general terms for the sometimes overly complex specialized ophthalmic terminology.

Classification of disease as it occurs in the eye has been notably simplified. In areas where etiologic classification cannot be accurately utilized, a morphologic classification has been adopted. With the exception of those types of endogenous uveitis with rather specific morphologic characteristics, such as tuberculosis and syphilis, all endogenous uveitis has been grouped under the granulomatous and nongranulomatous types. Similarly, in the section on the conjunctiva and cornea, the general reactions of these structures to numerous types of insult have been grouped together as morphologically indistinguishable. Retinoblastomas also

have been treated in the same fashion. A brief review of the background of this type of tumor is given, but until further knowledge of the origin of these tumors is available, the authors prefer to refer to them as retinoblastomas without rosettes and retinoblastomas with rosettes.

In a field which has until now been lacking in adequate texts, this new volume will make a welcome addition. Its simplicity of form, up-to-date approach, and beautiful illustrations will answer a long-felt need.

Le trachome. By Roger Nataf. Price, 3,700 francs. Pp. 426, with 46 figures. Paris, Masson & Cie, 120 Boulevard Saint-Germain, 1952.

This monograph is an authoritative review of the subject of trachoma by one of the world's foremost authorities, who has spent 25 years in studying this disease. Much of his work was done in the Pasteur Institute at Tunis.

The book covers the entire field of trachoma, with chapters on the history of the disease, its epidemiology and geographical distribution, its diagnostic aspects, pathology, and, finally, treatment. At the end there is a very extensive bibliography.

The author considers that trachoma is produced by rickettsial organisms belonging to the group of the Chlamydozoa, and that it should be designated Chlamydozoon trachomatis. This may well be the last authoritative monograph to appear on this dread disease, which mankind now seems to be in the process of conquering.

Surgery of the Eye. By Meyer Wiener, M.D., and Harold G. Scheie, M.D., D.Sc., F.A.C.S. Price, $15. Pp. 449, with 447 illustrations. Grune & Stratton, Inc., 381 4th Ave., New York 16, 1952.

The third edition of this popular textbook has been revised and partially rewritten. Dr. Harold G. Scheie, its new co-author, has contributed freely from his large experience to the first five chapters to add materially to the value of this volume. The discussion of the basic techniques in ophthalmic surgery contains many helpful hints, including clear descriptions of the methods of retraction of the eyelids, selection of instruments, and the technique of re-formation of the anterior chamber by the injection of air or saline. Anesthesia and preoperative and postoperative care are well presented. Cataract surgery is then discussed, with adequate illustrations clearly portraying not only the authors' technique but also other accepted methods. Following this is an unbiased presentation of the treatment of postoperative complications, with a frank expression of preference for certain procedures. In the chapter on glaucoma surgery the present-day concept of the two types of this disease is concisely given, along with the surgical treatment of each of them. This well-written section, which represents the greatest change in the volume, is its most important addition. In the chapter on detachment of the retina the operation of electrocoagulation is well described, but no mention is made of the technique of scleral resection. In the remaining nine chapters one finds but few changes, the most noticeable one being the addition of the Blaskovics operation for ptosis.

There is a lack of uniformity in the text, which is excellent in places and deficient in others—a defect which should be remedied in future editions. The printing is clear; the illustrations are good, and the format of the volume is pleasing. It is easy to read and contains much valuable information, with only a minimal number of controversial statements. It can be recommended as a text and will serve as a useful reference work to all ophthalmic surgeons.

Image Jump in Bifocals Can Be Alleviated

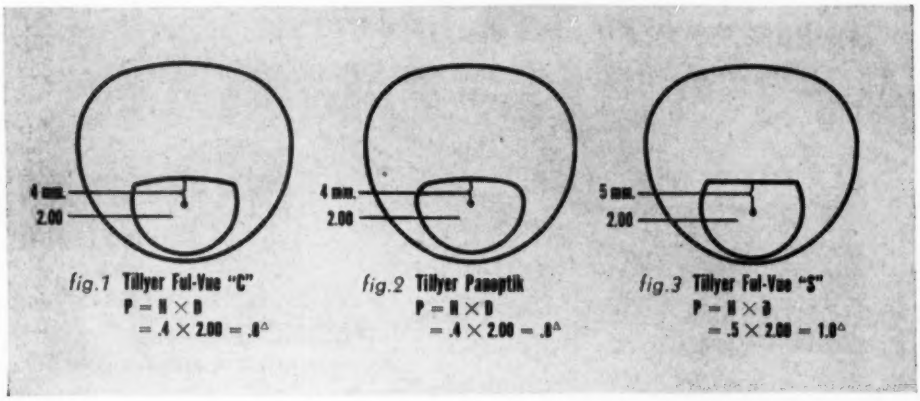

fig.1 Tillyer Ful-Vue "C"
P = H × D
= .4 × 2.00 = .8△

fig.2 Tillyer Panoptik
P = H × D
= .4 × 2.00 = .8△

fig.3 Tillyer Ful-Vue "S"
P = H × D
= .5 × 2.00 = 1.0△

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Image Jump refers to the prismatic conditions at the top line of a bifocal segment. If, at this point, there is a difference between the prismatic powers of the segment and the distance portion of the lens, there will be image jump.

Using Prentice's Rule we find that image jump is the product of the *dioptric* power of the reading segment times the *distance* of the segment's top line to its optical center. This rule reads P = H X D, where P = prismatic power in △; H = *distance* in centimeters from optical center to point under consideration; and D = dioptric power of the addition.

Comparison of bifocal types shown above indicates that, where image jump is a factor, the cut-off type segments are more satisfactory. Other segment types, of course, have a definite place in ophthalmic corrective measures.

A more complete discussion of Image Jump is available upon request. Write for your copy to Lens Sales Department at Southbridge, Massachusetts.

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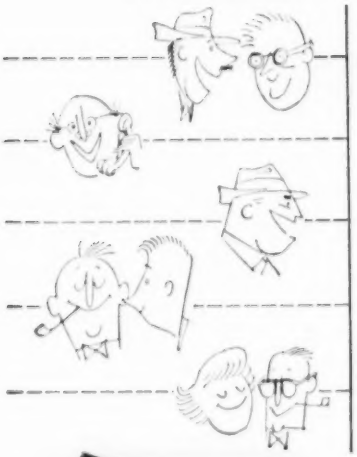

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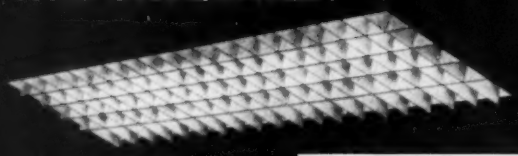

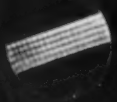

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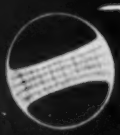

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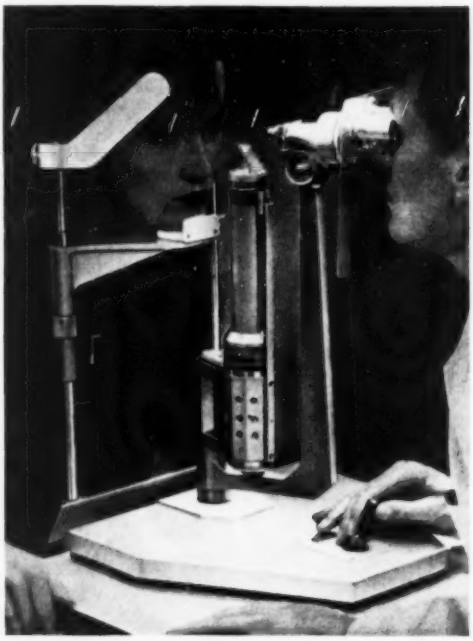

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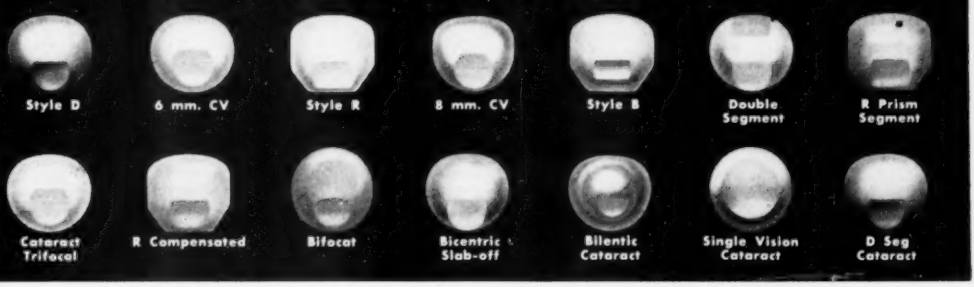

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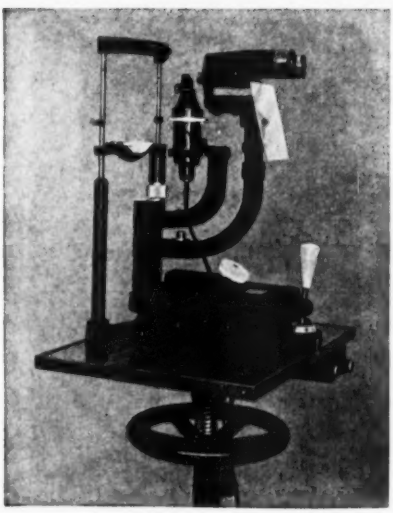

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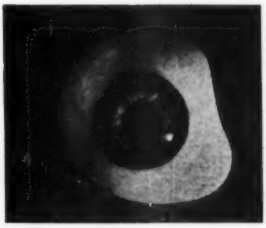

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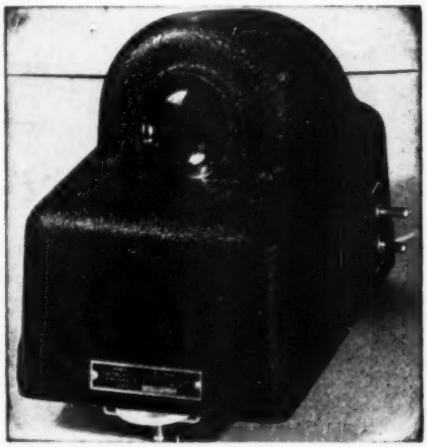

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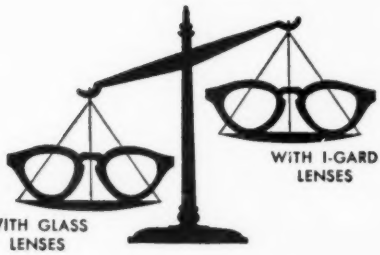

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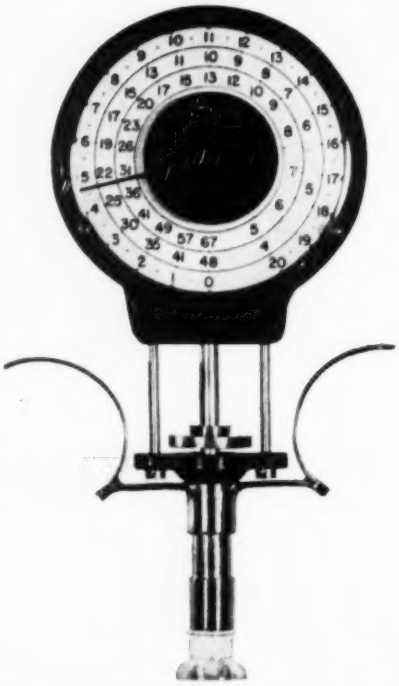

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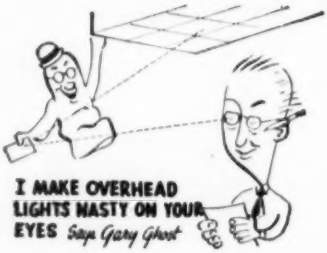

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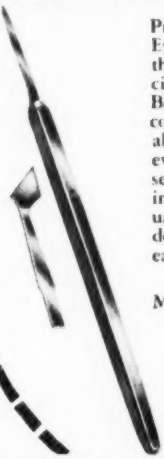

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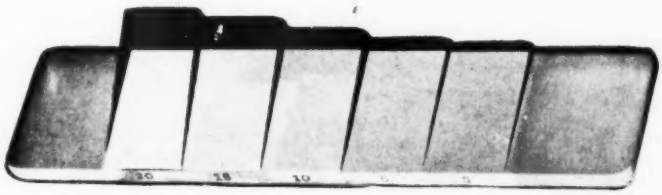

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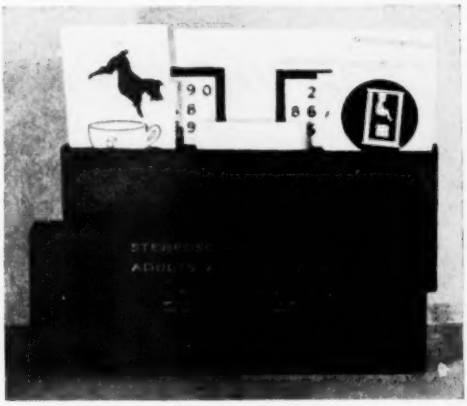

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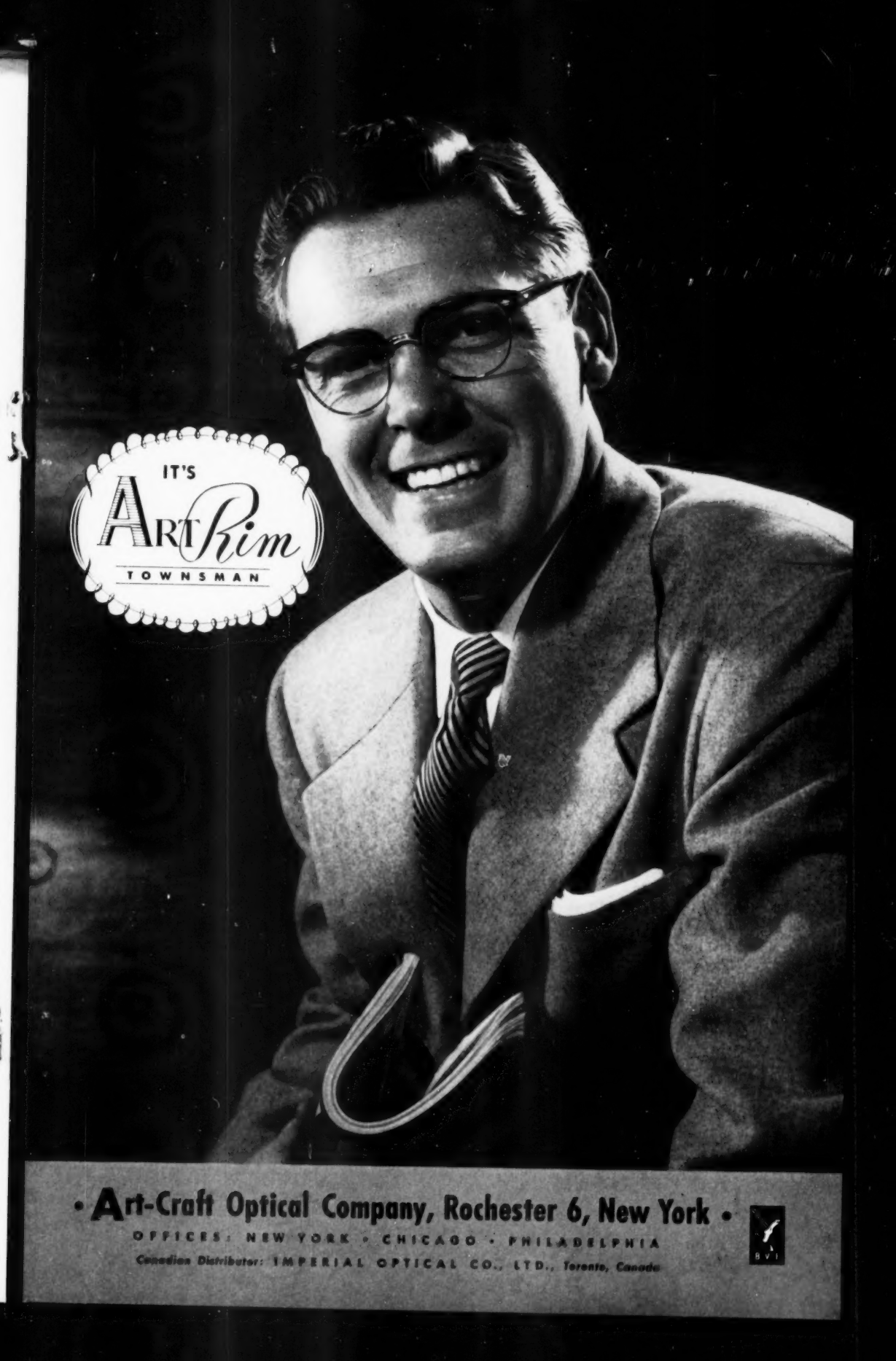

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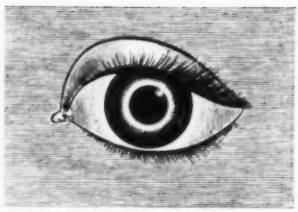

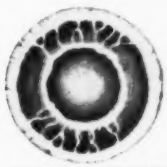

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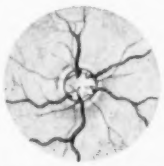

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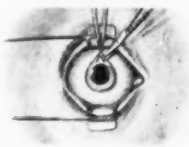

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